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University of Pennsylvania
School of Medicine

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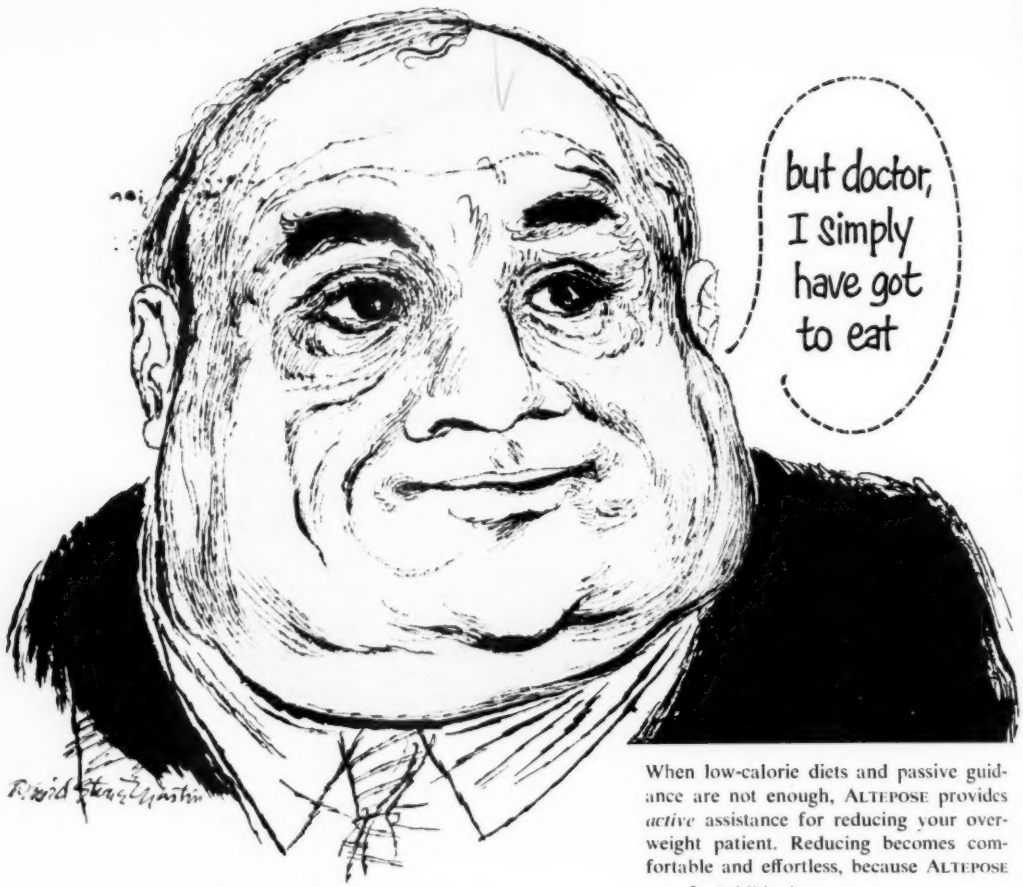

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References: 1. Jolliffe, N.: Reduce and *Stay* Reduced, Simon and Schuster, New York, 1952, p. 2. **2.** Tainter, M. L.: J. Nutrition 27:89, Jan. 1944. **3.** Kalb, S. W.: M. Soc. New Jersey 39:584, Nov. 1942.

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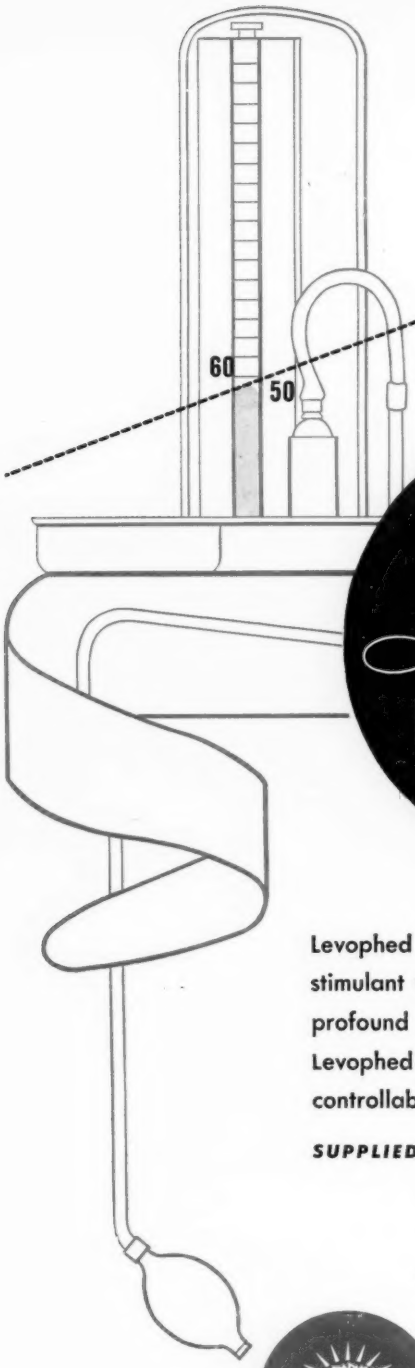

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants.

• FRACTURE OF THE FEMUR

Question: What would be the best method of open reduction in a dual fracture of the femur? The patient is a 59 year old man. The two fragments are widely separated.

M.D.—Michigan

ANSWER: The best method would be the type of internal fixation with which the surgeon is most familiar. This dual fracture of the femur would lend itself well to an intramedullary pin. If the distal fracture were in the mid-third of the femur, for a surgeon unfamiliar with intramedullary fixation, the use of the Eggers slotted plate at each fracture site would be indicated, and the femur would be encased in a light, long plaster spica. If the fragments were not widely separated, the more conservative skeletal traction would be given due consideration.

ROBERT D. SCHROCK

• HYALURONIDASE

Question: Will you please tell me where I can obtain the type of injectable material which is used to reduce renal stones. A patient of mine read an article on the subject, and he is interested in whether it would do anything for him before he decides to be operated on for stone. I would appreciate any information with regard to indications and contraindications.

M.D.—Missouri

ANSWER: The product being used for this purpose is hyaluronidase, which is marketed under several different trade names by various pharmaceutical manufacturers. This material is injectable, but I would certainly insist on having the complete instructions with the material that you purchase, so that you are able to make the solution or suspension properly and then inject it, keeping in mind the indications and contraindications specified with each package.

GILBERT J. THOMAS

• ELECTROLYTE IMBALANCE

Question: My patient is a 53 year old woman who, although she has never been in good health, yet has maintained a fairly good state of nutrition through the years. She has had 11 abdominal operations, but none of these was done during the past 12 or 15 years. I have hospitalized her three times during the past six months because of recurrent colitis with diarrhea. Roentgenograms revealed dumping syndrome—subtotal gastrectomy was done 15 years ago. The last time she was in the hospital I had a surgical consultation, and the surgeon's impression was chemical electrolyte imbalance plus a psychic disturbance. The symptoms were relieved when the patient was given Ringer's solution intravenously and enteric ammonium chloride by mouth.

Since returning to her home the patient has had some recurrence of colitis and diarrhea. The essential problem is how to maintain proper chemical and electrolyte balance at home without the use of intravenous therapy. Any suggestions as to further treatment would be much appreciated.

M.D.—Ontario

ANSWER: A woman 53 years old in a good state of nutrition with a history of multiple operations but no operations for 12 or 15 years should not have a dumping syndrome and, if present, it should not be the cause of symptoms. Instead, it would seem wise to do a careful serial study of the small intestine to determine whether there is disease of the small intestine which might produce chemical electrolyte imbalance and abdominal symptoms which could be attributed to psychic causes. If careful motility studies of the small intestine show no deviation from normal, barium enema studies and proctoscopic examination are indicated to rule out possible colitis.

Inasmuch as the treatment at home will depend entirely on the results of these observations, advice regarding treatment is best withheld for the present.

RICHARD B. CATTELL

(Continued on page A-36)

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• TRANSPLANTATION OF KIDNEY

Question: A few years ago, it seems to me, there was much in the press about a woman in Chicago in whom a physician transplanted a kidney from another woman who had died in an accident. Recently I read that a young man in Paris had had a kidney transplanted and that after a few weeks, during which time the transplant did not function, the young man died. Is there any record of successful transplantation of a kidney and is there any hope that this will ever be successfully accomplished?

M.D.—North Dakota

ANSWER: Kidneys have been transplanted and have functioned satisfactorily for a short period of time. There is some factor regarding the normal physiology of the kidney, i.e., a substance that it secretes or excretes, that is not apparent in transplanted kidneys. Since the nerves and/or the normal nerve supply of the various types is not re-established in transplanted kidneys, it is possible that this is the lack that causes disturbed function and eventually death of the kidney and/or the host. The character of the urine that is excreted or secreted by such a kidney gradually deteriorates and the product from the transplanted kidney is not the same as obtained from the normal-placed kidney. There is hope that this can be successfully accomplished in time, because we are constantly learning new facts about kidneys that are transplanted and why they do not function continuously as normal kidneys do. Whether we will be successful, eventually, I do not know. However, more difficult problems have been solved and I hope that this one will be as well.

GILBERT J. THOMAS

• BLOOD CHEMISTRY DETERMINATIONS

Question: Please list the indications for withholding food and medication prior to blood chemistry determinations. In general, is there any reason to withhold routine or special medication when performing, for instance, a nonprotein nitrogen determination?

M.D.—Virginia

ANSWER: The only blood chemistry determinations which are usually not considered to be affected by eating are creatinine, nonprotein nitrogen, urea and uric acid. Because of the postprandial absorption of amino acids, the nonprotein nitrogen level may be slightly affected but not usually within clinical ranges. Other than these substances, the levels of most laboratory tests of clinical interest are altered by food and by some medications. Some determinations may be interpreted adequately enough to be useful if the time after eating is known, but in most instances it is best to work with fasting specimens. Obvious examples of medications which would affect laboratory tests would include vitamin K, DICUMAROL®, intravenous potassium chloride, and insulin.

Blood sugar levels are frequently as useful when taken postprandially as when taken in the fasting state. Instances in which the response is more irregular due either to irregular absorption or to variation in the dietary intake cannot be interpreted as easily. These include calcium, chlorides, potassium, sodium and phosphorus. In addition, the results of procedures for amylase and phosphatase are affected by the glucose level of the blood. Some determinations cannot be carried out using chylous serum or plasma. Examples of this group are the icterus index, BROMSULPHALEIN® retention test, and serum proteins.

J. W. KING

• BRONCHOPNEUMONIA IN INFANT

Question: 1. May isopropyl alcohol be safely used to cleanse the skin of an infant prior to needle puncture?

2. When penicillin fails to cause improvement in an infant 2 months old suffering with bronchopneumonia, what type of procedure would you recommend?

M.D.—Illinois

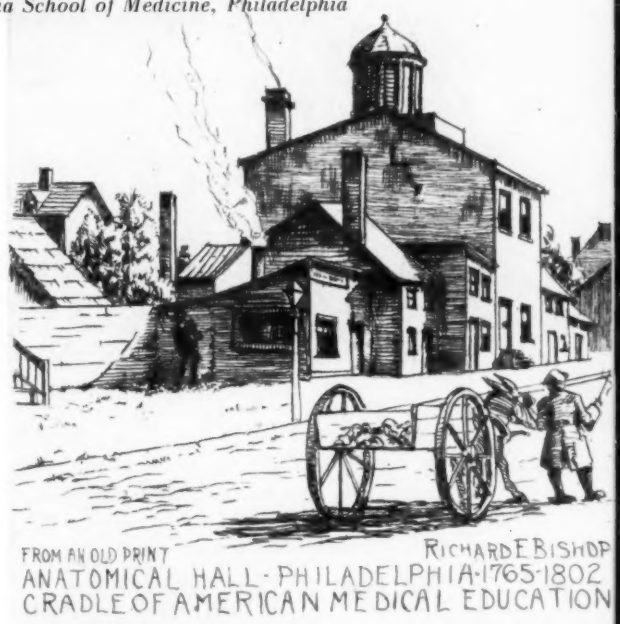
ANSWER: 1. Yes.

2. If blood cultures and cultures of the nasopharyngeal secretions and a roentgenogram of the thorax have been obtained and do not reveal any specific etiologic organisms or other signs, then one of the broad spectrum antibiotic agents, such as terramycin, could be used. If a definite organism has been isolated, then the appropriate antibiotic agent can be used. For staphylococcic infections, erythromycin should prove highly effective.

A Historical Sketch of the School of Medicine of the University of Pennsylvania

EDWARD B. KRUMBHAAR*

University of Pennsylvania School of Medicine, Philadelphia



An advertisement in the 1765 Pennsylvania Gazette *described the course as follows: "Dr. Shippen's course of Anatomical Lectures will begin on Thursday, the 14th of November, 1765. It will consist of sixty lectures, in which the situation, figure and structure of all parts of the Human Body will be demonstrated on the fresh subject; their respective uses explained, and their Diseases, with the Indications and Methods of Cure, briefly treated of; all the necessary Operations in Surgery will be performed, a course of Bandages given, and the whole will conclude with a few plain and general directions in the Practice of Midwifery. Each person to pay six Pistoles."*

A FEW lines may first be devoted to the condition of medical education and practice in the mid-eighteenth century colonies preceding the inauguration of organized medical teaching. As in all new countries, the healing art had for many years been practiced along the Atlantic seaboard, not only by the few physicians who had come over with the original colonists but also by clergymen, plantation owners and many other intelligent citizens such as the members of the American Philosophical Society (1744), by barbers, carpenters and others down to the lowest grades of quacks and impostors. There was, however, an increasing class of "apprentices" who learned the art by aiding established practitioners, sometimes for five or six years.

As wealth accumulated in the growing country, young men in increasing numbers went to European schools, especially Leyden and Edinburgh. Thus Morgan and Shippen, founders of the medical department of the College of Philadelphia (later the University of Pennsylvania), both had Edinburgh degrees. Benjamin Rush, after serving as apprentice to the elder Shippen for seven years, graduated from Edinburgh in 1769, and Adam Kuhn, the fourth member of the first faculty, graduated

*This survey of the oldest medical school in the United States was requested as an appropriate introduction to the series of articles in this issue written by Pennsylvania men.

The School is at times incorrectly designated as the oldest in America, perhaps in ignorance of several founded much earlier in Latin America, e.g., in Mexico (1580), Lima (1621), Caracas (1721), Havana (1726), Bogotá (1758). Mexico being generally regarded as a part of North America, our School's priority is best regarded as limited to the United States.

there in 1767. It is noteworthy that this famous school was itself less than 50 years old at the time.

EDWARD B. KRUMBHAAR

The story of the steps leading to the founding of the Medical School is well known[1-4]—Morgan and Shippen's plans discussed together while studying abroad, Shippen's courses in anatomy and midwifery on his return, as announced in the *Pennsylvania Gazette* in 1762, Fothergill's gift of the anatomic crayons the next year for Shippen's use at the Pennsylvania Hospital, where rich clinical material had been used for teaching for a decade, and finally Morgan's proposal to the trustees of the College of Philadelphia for a medical department the month after his return home in April 1765. His "Discourse upon the institution of medical schools in America" is justly accepted as an important milestone in the history of American medical education. Shippen, who had been elected professor of anatomy and surgery in September 1765, announced that his lectures would begin on November 14, though according to Carson and Packard they actually began on September 18, 1766. Morgan, as professor of the theory and practice of physic, announced his course for November 18, but it actually began, again according to Carson and Packard, on September 26, 1766.

Organized medical instruction in institutions of higher learning found favor in New York about the same time as in Philadelphia.[4] The Medical School of King's College (now the College of Physicians and Surgeons of Columbia University) was organized in 1767 with a faculty of six and gave its first degrees of Bachelor of Medicine in 1769 and the Doctorate in 1770. The Pennsylvania M.B. was given in 1768 but the M.D. was not given until 1771, so that P. & S. can rightfully claim the earliest doctorate degree given in course in this country.

On November 26, 1766, Thomas Bond, a founder of the Pennsylvania Hospital, instituted the first regular course of clinical lectures with a discourse on their utility before the managers and staff (publicly delivered on December 3, 1766).[5] These were continued until his death in 1784, and though Bond was officially requested by the School's trustees to continue them, he seems never to have been given a position on the School's faculty. It should be added that though clinical teaching languished in all American schools for many decades, it was never abandoned at the Pennsylvania Hospital and was always available to the University's students.

It must be remembered that the College was located at this time on Fourth Street, so that the hospital was within easy walking distance. When clinical instruction came to the fore again in the latter part of the nineteenth century, the University's medical students were sent for clinical work to several of the city's hospitals. This practice still continues, though some—the Pennsylvania and Episcopal for instance—are distant from the new location in West Philadelphia.

Returning to the early days of the school, didactic medical teaching was given successfully in the College halls at Fourth and Arch for several years.[2] Anatomy and chemistry were soon moved to the Anatomy Building on Fifth Street, and after the ructions of the Revolution had been healed they were moved again to the so-called "President's House" on Ninth Street, at which site a new building was erected for the Medical School. Here it was to remain till the move to West Philadelphia in 1872.

To the company of Morgan and Shippen, Adam Kuhn, a pupil of Linnaeus, was added in 1768 as professor of botany and materia medica, and in 1769 Benjamin Rush, then aged 24, as professor of chemistry. This "original faculty" continued unchanged until 1789, when the "Institutes of Medicine" (i.e., physiology) was taken out of the theory and practice of medicine as an independent chair for Caspar Wistar. Anatomy was not separated from surgery till Physick was made professor of surgery in 1805.

Classes at first were small: At the first

medical commencement (1768), which the trustees spoke of as "the birthday of medical honors in America," degrees of Bachelor of Medicine were given to eight men whose names may be found inscribed on a bronze tablet in the medical laboratories. Following the custom abroad, the degree of Bachelor of Medicine for some years was given at graduation and the Doctor's degree a few years later on completion of a thesis and payment of a fee. However, very few bothered to take it, though even the doctorate demanded but two years' attendance at lectures together with three years' apprenticeship to a recognized practitioner. The apprentice, who assisted his master on his rounds, in making up prescriptions, preparing bandages and so on, paid handsomely for the privilege. Benjamin Rush said in 1791 that his usual fee was £ 100 cash. The bachelor's degree was abolished at Penn about the year 1790. According to Cheyney,[2] the M.D. was the only medical degree to be given in America after 1791. By 1800 there were five medical schools in existence in this country, but the oldest of them seems to have been the recognized leader; Mumford, for instance, speaks of New Englanders making a two or three week journey on horseback in order to study at the Philadelphia School.

The number of those graduating each year at the University was small in relation to the number of matriculants—for some time fewer than one in eight (8 out of 60 for instance, in 1784; 15 out of 150 in 1804). In the 20 years from 1809 to 1829, with the number of students in the two year course averaging over 400, those graduating averaged 88 per year. More than half came from the South—and at times more from Virginia than from Pennsylvania—while of the 123 M.D.'s in Georgia in the first quarter of the nineteenth century, about two-thirds came from the University.

A student's expenses were not great—under $500 a year—and included fees of about $20 to each of the five or six professors whose courses he attended, tickets of admission to the hospital wards and library, and $30 to $40 for graduation expenses. It is interesting to note in passing that as far back as 1822, fees of attendance were remitted by the University to six needy students annually. The School, which was bigger than the College, enjoyed much autonomy under the Dean, a rotating office until Horner became permanent Dean in 1822 and so continued for 30 years. Board and lodging cost about $5 a week for the term of three months. A student in 1816 tells, in a letter to his father[6] soon after arrival, of attending "six professors in the day, each of them lecturing an hour, five of them before dinner"—but that he could not "take the ticket" of either the Hospital (Pennsylvania) or the Almshouse (the future Philadelphia General) for want of money. He also would "need some money for the purpose of getting a subject to dissect."

As "personalities make news," much could be said about the outstanding names on the faculty during its first hundred years. Limitations of space, however, permit nothing more than a bare list: Morgan, Shippen, Kuhn and Rush, all eminent, have already been mentioned; others were Caspar Wistar, of Wistaria and Wistar Party fame; the three Bartons, two botanists and a surgeon; James Hutchinson, a martyr of the 1793 yellow fever epidemic; Physick, "the Father of American Surgery"; Nathaniel Chapmen, successful lecturer and editor; Horner, whose *tensor tarsi* is a term still retained in use; G. W. Norris, eminent surgeon in pre-antiseptic days, medical historian and first of a prominent medical family; George B. Wood, a copious author, editor of the United States *Dispensatory*, also founder of another Philadelphia medical family; Robert Hare, "one of the most eminent chemists of his time"; Agnew, the leading American surgeon of his day; Leidy, the most distinguished biologist in the whole University's history.

The comparative overemphasis on lectures and neglect of clinical and laboratory work were common to all medical schools in this country and continued throughout most of the century.* In fact, if Norwood's[3] estimate of

*The little known growth of laboratories before they reached the dignity of departmental rank offers an attractive field for some historical research. Cheyney speaks of laboratories not only of chemistry and anatomy, but of physiology, pharmacy and histology, even before 1870, "though where these laboratories were tucked away remains a mystery."[2]

Pennsylvania's influence on medical education in this country is correct, our School must accept a large share of the responsibility for this trend. Strange, too, to us in the twentieth century was the shortness of the two year course, from November to commencement in March; presumably, many students worked as apprentices or their equivalent during much of the rest of the year.

It should not be thought that clinical instruction had been entirely abandoned, however, in this "low water" period of medical education. In fact, in the Report on the Medical Department for 1845 by the Faculty to the Alumni,[7] clinical teaching was stressed, having been facilitated by the organization of a University dispensary and clinic. The wards of the Pennsylvania Hospital were always open to medical students, as were, most of the time, those of the adjacent Philadelphia Almshouse.

In 1865 the subjects taught were further supplemented by the creation of an auxiliary School of Medicine with courses in zoology and comparative anatomy, botany, mineralogy and geology, hygiene, medical jurisprudence and toxicology. These courses, which were free to medical students, were immediately successful, with 436 matriculated in 1877, some receiving first the degree of Doctor of Philosophy, later changed to a Bachelor of Sciences Auxiliary to Medicine. By 1898, when the regular medical course had been lengthened and expanded, the school had been abandoned and courses such as hygiene and legal medicine incorporated into the general course.

The move of the whole University to West Philadelphia in the early seventies occurred at a time when medical instruction generally was ripe for change and expansion. The leading part played in this development, at Harvard by Charles W. Eliot, the new president, and at Pennsylvania under Stillé's provostship by a group led by his future successor (1881), William Pepper, is insufficiently known—perhaps obscured by the brilliant achievements at Johns Hopkins in the next decade. In West Philadelphia the new medical school (at present Logan Hall) and the University Hospital (the first to be built anywhere in the world primarily for the education of students) were occupied in 1874. The next year it was proposed that the course be extended to three years, with a teaching year of four months (!) and that student fees ($140 the first two years and $100 for the third) be paid to the University, the professors to receive fixed salaries.[8] It is interesting to note that in the very early days with a small faculty, professors received as high as $8000 a year in students' fees. Later, however, this figure fell to from $2000 to $3000, so that professorial salaries were fixed at $3000. Cheyney states that the total budget was estimated at $11,000 (exclusive of salaries).

It is significant in this connection that, as may be seen in Louis Schmidt's illustrated Roll of Professorial Chairs (hanging by the Dean's office in the Medical School), the number of chairs in the Medical School was almost doubled in 1874 and 1875 (clinical medicine; diseases of the ear, of the eye, of women and children, of the nervous system; pathology; dermatology) and another seven had been added by 1903 (pediatrics, genitourinary diseases, hygiene and bacteriology, orthopedic surgery, mental diseases, neuropathology, laryngology and rhinology).

The deficiencies in medical education pointed out by William Pepper (at the time, professor of medicine) in his address on "Higher Medical Education" (1877) have taken a long time to make up. Since then, new wants have appeared as the field expanded; but much was accomplished before the end of Pepper's provostship in 1894. A department of hygiene with its own building, an endowed professorship and John S. Billings as director was forthcoming in 1892—the first of its kind in the United States. In 1895, the William Pepper Laboratory of Clinical Medicine was founded by Dr. Pepper in memory of his father, who was professor of medicine in the sixties. Also the first of its kind in the United States, it was designed, at a time when laboratory research on clinical material was in its infancy, to be a subsidiary of the hospital yet independent in its management and type of work. Changing with the times—now almost

every department in the medical school has its research division or special institute—the Pepper Laboratory combines with its research all the routine laboratory work for the hospital not done in the wards.

The hospital has grown steadily during its 78 years with a bewildering number of new wings and institutes (Musser Department of Research Medicine, Harrison Department of Surgical Research, Johnson, Robinette and Donner Foundations, and the Cox Institute, to name the more important). Greatest of all, the Gates Memorial Pavilion and Diagnostic Clinic is now approaching completion, dominating the University landscape in massive, functional beauty.

With the turn of the century, the old story of inadequate space in a rapidly growing institution had again become pressing. The "new medical laboratories" were built in 1904 (with a wing added in 1909) to house the preclinical departments. The Scotch thistle over the entrance symbolizes the parentage of the Edinburgh School, with the names of the original faculty carved on surrounding medallions. Eakin's massive painting of Agnew performing an operation before the class in surgery faces the visitor as he enters, while in its corridors, lecture rooms and library hang oil portraits of practically all the School's professors since 1765.

The frequent repetition in this article of terms like "the first of its kind" should not convey the suggestion that the School is in any way resting on its oars. Rarely does a year go by without some important change, some of which, like the Undergraduate Medical Association (founded 1908), which now has its own *News*, have pioneered similar activities in a number of the schools of this country. Two years ago occurred a reversal of the time-honored arrangement of third and fourth year work; now the third year is spent mostly in the wards, the fourth year, more logically, in the outpatient departments. Even more important in these days of extreme specialization is the plan of introducing a student into a family to take a responsible and increasing share in that family's health care during his entire four years. In this connection it is not without interest that, according to Norwood, the 1845 Report previously cited referred to the students' privilege of treating patients in their homes. The Family Health Advisor service is augmented in the first year by lectures introductory to clinical medicine and a series of seminars in which studies are correlated with the actual patient, all of the hospital's specialists participating.

We like to agree with Norwood that "the University of Pennsylvania was eminently successful in the performance of its mission as the first and foremost medical school in the English colonies of America and the United States" and that it "maintained its position of leadership in medical education at least until the middle of the century." Increasing competition, however, has long since so changed things that no one school would want to make such a claim today. To be among the best is sufficient honor.

This attempt to trace in some of its activities the development of one of our leading medical schools now is brought to a close. Many aspects have necessarily been neglected, others told incompletely. If the story should have any value to medical educators or interest to Pennsylvania men, the writer will be well satisfied.

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Antimicrobial Therapy of Bacterial Pneumonias

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With the advent of the antimicrobial agents, the mortality and morbidity rates due to bacterial pneumonias have been markedly reduced. Nevertheless, bacterial pneumonia remains a serious disease, especially in patients more than 50 years of age and those having chronic illnesses. For the most part, penicillin, administered in any of a variety of preparations and dosages, is the drug of choice for the treatment of this disease. In patients with recurrent pneumonias the likelihood of bronchial disease is strong and a search for underlying factors must be made.

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THE importance of pneumonia needs no emphasis to the physician, for irrespective of his particular field of medical practice, it is a disease with which he must deal. Although a larger proportion of cases of milder atypical pneumonias is now recognized and the mortality from classic pneumococcal pneumonia has dropped strikingly, there is still a significant mortality from bacterial pneumonia, particularly among the aged. The practice of medicine offers no greater satisfaction than the successful treatment of a severe pneumonia which, prior to modern antimicrobial therapy, proved highly or uniformly fatal. Early and accurate diagnosis, followed by the proper use of these agents, leads directly to this earned reward.

Classification of a Bacterial Pneumonia

Pneumonia is no longer considered a single disease entity, but rather a group of specific infections with a common denominator, namely an exudative inflammation involving one or more lobes of the lung. From the standpoint of management, it matters little whether the pneumonia is lobular or lobar, but it is essential to determine the causative organisms. Hence, for this discussion I shall employ a classification based on etiology, rather than on a basis of anatomic distribution or pathologic character. Bacterial pneumonias have been grouped into three main types in Table 1. The first group comprises the so-called primary pneumonias, of which pneumococcal pneumonia is the prototype. Although classic pneumococcal pneumonia appears to be diminishing in frequency, the *Pneumococcus* still remains the commonest invader of the lungs. In the second group are included the few bacterial pneumonias which are the result of systemic infection. There has been in recent years a striking decline in incidence of pneumonias of the first group,[1] and the third group has become the most numerous and most important, including as it does infections secondary to disturbances of pulmonary function produced by bronchial obstruction, atelectasis, aspiration, stasis and the like.

Early Diagnosis of Pneumonia

The length of time that elapses between the onset of pneumonia and the beginning of treatment is of great importance, especially in persons over the age of 50 years and those with heart disease, tuberculosis, diabetes mellitus, alcoholism, or similar chronic diseases. Hence, one should institute therapy as soon

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TABLE 1

ETIOLOGIC CLASSIFICATION OF BACTERIAL PNEUMONIAS WITH RECOMMENDATIONS AS TO TREATMENT OF CHOICE

	ANTIBIOTIC				
	Penicillin	*Streptomycin*	*Aureomycin*	*Terramycin*	*Chloramphenicol*
I. Specific pneumonia					
A. Coccal					
Pneumococcal	I		I	I	
Streptococcal	I		I	I	
Staphylococcal	Ic		Ic	Ic	Ic
B. Bacillary					
H. influenzae		II	I		
Bacillus mucosus capsulatus		I	II		
Mycobacterium tuberculosis		I+			
II. Systemic disease with pneumonia					
Eberthella typhosa					I
Pasteurella tularensis		II	I		
Past. pestis			I		
Brucella group		Ic	Ic		
III. Pneumonia, secondary to various factors (bronchial obstruction, atelectasis, aspiration, stasis, etc.)					
Mixed infections	II		I	I	

I . . . first choice.
II . . . second choice.
c . . . combined therapy.
+ . . . with PAS.

as the clinical diagnosis has been made and the necessary material has been collected for laboratory study. In a number of cases of pneumonia, it is impossible to be sure of the diagnosis when the patient is seen for the first time. Although antibiotic therapy need not be withheld until a bacterial diagnosis has been established, there are occasions when it is justifiable to wait for further developments in order to arrive at a more accurate diagnosis or to see if the condition will not improve spontaneously. Not only does this give the disease an opportunity to manifest itself more definitely, but also it eliminates the possibility of drug toxicity. Likewise, it is sometimes advisable to discontinue all chemotherapy, particularly in the patients in whom the response has been unsatisfactory and in whom the diagnosis is uncertain.

Accurate Diagnosis of Pneumonia

As a result of the effectiveness of the new therapeutic agents, there has been a definite trend toward carelessness in diagnosis from both a clinical and laboratory standpoint. Obviously, there are many pneumonias which respond dramatically to the antibiotics without an accurate diagnosis. In some instances, the causative organism can be accurately recognized without laboratory aid, by virtue of the characteristic clinical picture of the disease. In certain instances, however, the diagnosis to a large extent is one of exclusion and in such cases it is often necessary to accumulate considerable clinical, laboratory and roentgenographic data. It is in this group that the proper selection of laboratory tests, together with an adequate history and physical examination, aids greatly in establishing an accurate diagnosis.

1. Etiologic diagnosis—In view of the action of the antibiotic drugs, the determination of the causative agent is the most important single factor in the successful management of pneumonia patients. Unfortunately, the wide therapeutic range of these drugs has resulted in failure in most instances to establish an etiologic diagnosis. Usually, the necessary laboratory studies, such as blood and sputum cultures, complete blood count, and chest x-ray, are reserved for cases failing to respond to therapy. For this reason, accurate figures

dealing with the treatment of large groups of pneumonias are becoming increasingly difficult to assemble and as a consequence data regarding the use of the newer antibiotics are limited. Although these newer drugs possess a broader spectrum of activity, certain patterns have developed which demonstrate the fact that certain groups of bacteria are more easily controlled by different antibiotics. For example, certain strains of Friedländer's are more sensitive to AUREOMYCIN® than to streptomycin. Many strains of staphylococci are resistant to penicillin, but will respond to aureomycin and terramycin. Typhoid infections are best treated with chloramphenicol. Not infrequently, a unique situation exists wherein an antibiotic with a limited range of activity is the best drug for an infection, such as polymyxin in *Pseudomonas* infection.

In other words, successful antibiotic therapy is becoming a more specific form of treatment and depends to a certain degree on specificity of action—hence, the importance of knowing the causative agent in each infection in order to administer the most suitable antibiotic. Theoretically, this should be done routinely, but from a practical standpoint this is difficult to carry out. Therefore, there must be some middle road between the practice of giving antibiotics indiscriminately to every pneumonia suspect and that of withholding antibiotic therapy until a definite diagnosis is established. Certainly, all serious pneumonias, especially those occurring in individuals over 50 years of age and with certain chronic diseases, and those infections which fail to respond satisfactorily, demand efforts on our part to establish an etiologic diagnosis.

Once the organism has been isolated, antibiotic therapy can be selected intelligently for most infections without resorting to sensitivity tests, except when one is dealing with bacteria, different strains of which are known to exhibit wide variations in susceptibility to the antibiotics under consideration. It appears to be generally true that strains of pneumococci and group A hemolytic streptococci are quite uniform in their susceptibility to a given antibiotic. Other organisms, obviously, differ widely in their antibiotic sensitivity, such as staphylococci, enterococci, and Friedländer's organisms.

Although the determination of bacterial sensitivity to antibiotics is a procedure widely employed, it is one which is often misleading to the physician. The use of these tests is based on the assumption that the effectiveness of the various chemotherapeutic agents determined by in vitro tests parallels the therapeutic results of these agents. Clinical results are, of course, influenced by the degree to which the particular antibiotic is distributed in the body and it is a common experience that the therapeutic effectiveness differs from the results reported in in vitro tests. In this connection, the clinical activity of penicillin is especially likely to be underestimated in in vitro tests. Infections due to a strain only slightly susceptible to concentrations of penicillin employed in laboratory tests, and moderately or highly susceptible to other antibiotics, clinically may respond more rapidly to penicillin because of the higher blood and tissue concentrations readily obtainable with the latter drug. In general, it is wise to consider sensitivity tests as performed in the ordinary laboratory as only qualitative guides to distinguish susceptible from nonsusceptible organisms.

As indicated, a complete blood count, including hemoglobin determination, leukocyte count, and a differential enumeration of white blood cells should be done preferably before institution of specific therapy. A high initial white cell count which diminishes rather rapidly after 48 hours of treatment is usually of good prognostic import; while a persistently high or increasing count often indicates a spread in the infection or a complication of the disease. Patients with low initial counts are often seriously ill, but if they respond to treatment, the count will usually rise within several days. The failure of a low count to rise is generally a poor prognostic sign. Although the total white count is not diagnostic, it is often helpful in differentiating between bacterial and viral infections.

2. Clinical diagnosis—The diagnosis of pneumonia cannot be made merely from laboratory studies. It remains for the physician

to determine the etiology, not only from these findings but also from a detailed history and careful physical examination.

A. History taking—One of the most important steps in arriving at a diagnosis is to recognize and note the earliest symptoms of the disease. Often valuable information pertaining to the patient's illness can be elicited, not only from the patient, but also from other members of the family. The history of a preceding common cold; severe sore throat; an urban inhabitant drinking raw milk in the country; the removal of ticks from a dog in the late spring or early summer; recurrent bouts of furunculosis; trauma; contact with animals, and many other leads will often supply the needed information. Today, we are often too busy to take a detailed history.

B. Physical examination—It has been said facetiously, but with some degree of truth, that if a patient does not improve after 48 hours of antimicrobial therapy, a physical examination should be performed. Certainly, no patient should receive any therapy without first having a thorough physical examination. The physical findings of consolidation in a typical fully developed case of pneumococcal lobar pneumonia are characteristic, but seem to be infrequently encountered in recent years. In many cases physical examination reveals only impaired resonance or rales without classic bronchial breathing. Roentgenographic examination is desirable in order to demonstrate the extent or density of pulmonary involvement. The clinical and roentgenologic findings in the pneumonias due to various bacteria are rarely sufficiently characteristic to suggest the etiologic diagnosis. However, the classic history (sudden onset of chills and fever, pain in the side, cough and expectoration of rusty sputum) and the physical findings as described when encountered are, of course, suggestive of pneumococcal pneumonia. Furthermore, a history of a severe sore throat for several days preceding the pneumonia would suggest a streptococcal affair. The demonstration of multiple cavities by x-ray examination should direct suspicion toward staphylococci or Friedländer's bacilli as the causative agents.

As the frequency of primary bacterial pneumonia diminishes, it should be recognized that an ever increasing proportion of pneumonias will be found to be due to mixed infection, and in such cases it is mandatory that a search be made for underlying factors predisposing to pneumonia.[2] In every patient who has had recurrent attacks of pneumonia, especially if the same lobe has been repeatedly involved, the likelihood of bronchial disease is strong. Bronchiectasis, bronchial adenoma, bronchogenic carcinoma and atelectasis of other cause must be excluded in such cases. In an aging population, constant vigilance must be maintained for pulmonary neoplasm, which in its early stages may produce or simulate a pneumonic process.

Another disease increasing in frequency as a cause of chest pain, blood expectoration and fever is pulmonary infarction. In our experience, many so-called postoperative pneumonias are actually the result of embolism and a considerable proportion of pneumonias occurring under other circumstances prove to be infarctions.

Pleurisy with effusion would ordinarily appear easy to distinguish from pneumonia clinically or roentgenologically. Actually, on occasion, effusions and pneumonias may be taken for one another, despite meticulous physical examination and intensive x-ray study. Thoracentesis should be attempted whenever there is doubt.

Proper Use of Antimicrobial Agents

Penicillin—Penicillin, by virtue of its bactericidal action, remains the most effective antibiotic against the majority of bacterial infections and, since it is least expensive and toxic, it remains the drug of choice in the treatment of most of the bacterial pneumonias encountered in this part of the world. Certainly, very few lives will be lost by administering penicillin initially and, if subsequent clinical and laboratory studies of the disease are such as to demand it, then employing one of the other antibiotics. Penicillin continues to be the drug of choice for all gram-positive bacterial infections including pneumococcic, staphylococcic, and hemolytic and

nonhemolytic streptococcic infections. It would appear that penicillin in almost any dosage and form will give excellent results in the treatment of pneumonia due to penicillin-sensitive organisms.[3] The three schedules which appear most useful are the administration of aqueous crystalline penicillin (100,000 units every 8 to 12 hours), the daily injection of procaine penicillin preparations (300,000 units), or NEO-PENIL® (500,000 units).

The characteristics of the various penicillin preparations provide advantages for specific purposes. The use of procaine penicillin in aqueous suspension (300,000 units) once daily is less expensive than aqueous penicillin given at three or four hour intervals, and is adequate for many pneumonias. When such complications as meningitis or endocarditis are present, however, the low level concentrations afforded by procaine penicillin or neo-penil will not provide sufficient diffusion, and frequent intramuscular administration of aqueous crystalline penicillin (100,000 to 1,000,000 units) is indicated. In the home, the advantage is evident of using procaine penicillin with aluminum monostearate in oil (300,000 units) so that injections may be given at one or two day intervals. Also, under these circumstances, oral penicillin given at three hour intervals in doses of 200,000 units for the average adult provides effective plasma levels.

A recently introduced compound, benemid,[4] offers considerable promise of increasing the usefulness of oral penicillin in the treatment of pneumonia. This benzoic acid derivative, given in 0.5 gm. doses four times daily, exerts the same action in enhancing penicillin blood levels as was manifested by carinamide in much larger dosage. Benemid has been incorporated into the oral penicillin preparations in such fashion that a pill containing 200,000 units of penicillin and 0.5 gm. of benemid, taken every six hours, will produce sustained therapeutic levels in the blood.

Neo-penil—A new penicillin ester, neo-penil (the hydriodide of diethylaminoethyl ester of penicillin G, known generically as penethamate hydriodide), has been shown to produce higher concentrations of penicillin in certain body tissues or organs than do the commonly employed penicillin salts.[5,6] The concept of penicillin derivatives having affinity for certain tissues or organs of the body is not new, but this is the first instance in which the phenomenon has been observed to a degree that is therapeutically significant. Animal and human experiments have shown that neo-penil has a far greater affinity for the lungs than have the other penicillin preparations. Since these unusually high tissue concentrations occur in the absence of high blood levels it is felt that the tissue levels are due to the pharmacologic property of the drug and not merely to a high blood-tissue diffusion gradient.[7,8] During the past year, this new penicillin compound has been studied at the Philadelphia General Hospital and found to be highly effective in bacterial pneumonia.[9]

Streptomycin—The development of aureomycin, chloramphenicol and terramycin has to a significant degree diminished the importance of streptomycin (dihydrostreptomycin) as a therapeutic agent—except that streptomycin remains uniquely valuable for the treatment of tuberculosis and should be reserved for the same—except in those instances where it is used in conjunction with other antibiotics, or in resistant infections. Dosage schedules (0.5 to 2 gm. daily) vary according to type and severity of infection.

Aureomycin, chloramphenicol and terramycin—For the most part these newer chemotherapeutic agents have a similar range of antibacterial activity and are usually referred to as the wide spectrum antibiotics, namely, for certain virus diseases and rickettsiae, both gram-negative and gram-positive bacteria, including penicillin-resistant, streptomycin-resistant and streptomycin-dependent organisms. Which of these drugs is used is usually merely a matter of personal preference or habit, but it is important to recognize the few individual differences in behavior in this group as well as their potential toxic effects, especially chloramphenicol. Dosage for these drugs ranges from 2 to 4 gm. daily in divided doses every four to six hours.

It is to be remembered that whereas penicillin and streptomycin in adequate con-

centrations are bactericidal and in lower concentrations are bacteriostatic, the action of aureomycin, chloramphenicol and terramycin is merely bacteriostatic. As a consequence, administration of the latter agents should be continued several days longer after defervescence than is necessary with penicillin and streptomycin.

Drug Toxicity

The untoward reactions following antibiotic therapy are becoming increasingly familiar. Penicillin remains the least toxic of the now available antibiotics and, if the reactions are not too severe, treatment can usually be continued with the aid of many symptomatic and anti-allergic remedies. Obviously, the more serious reactions demand discontinuance of the drug. Many patients can tolerate penicillin even after a previous allergic reaction to the same, thus making difficult an evaluation of the so-called hypo-allergic penicillin preparations. Vertigo and deafness are the chief toxic reactions following streptomycin therapy. Fortunately, however, with the present day dosage schedule in combination with PAS employed in tuberculosis, this complication has been markedly reduced.

Aureomycin, terramycin and chloramphenicol frequently give rise to gastrointestinal disorders which at times may become quite severe. Chloramphenicol may cause certain fatal blood dyscrasias. However, until a better drug is developed for the treatment of typhoid fever and certain penicillin-resistant organisms, chloramphenicol will continue to have a definite place in our therapeutic armamentarium. It is felt that the gastrointestinal lesions are the result of altered bacterial flora which lead to a vitamin B deficiency. Hence, the advisability of administering liver extract intramuscularly and vitamin B complex orally in conjunction with the use of the wide spectrum antibiotics. The use of yogurt, acidophilus and buttermilk all are worth a trial in cases with these reactions. Obviously, when one considers the untoward reactions associated with these agents, it is essential that the physician who undertakes to prescribe these drugs shall exercise the same caution as when he administers any other highly useful but potentially dangerous drug.

Combined antibiotic therapy—It is frequent practice in the treatment of pneumonias to employ antibiotics in shotgun fashion. This practice has been furthered by the recognition that in certain instances a definite synergistic action, or additive effect, is obtainable from certain combinations—tuberculosis (streptomycin plus PAS); brucellosis (streptomycin plus aureomycin); enterococcic endocarditis (penicillin plus streptomycin); bacterial meningitis-staphylococcic, pneumococcic and streptococcic (penicillin plus sulfonamides; *Hemophilus influenzae* (streptomycin plus sulfonamides). Despite these examples, there are experimental and clinical studies which show that certain combinations result in antagonism and diminished effectiveness. Aureomycin, terramycin and chloramphenicol have been shown to diminish the effectiveness of penicillin. The interference is apparently due to the inhibition of multiplication of organisms produced by the bacteriostatic action of the wide spectrum antibiotics; the bactericidal action of penicillin is manifested only with rapidly multiplying organisms and hence penicillin activity is impaired by the concomitant use of these bacteriostatic agents. At this time it is evident that the problem of antibiotic synergism and antagonism is far from settled. Certainly, combined therapy should be restricted to the relatively few situations in which specific combinations are of established value. For the most part, combined antibiotic therapy is useful and indicated chiefly in chronic infections. There is no justification for the use of multiple agents in most acute infections and it is certainly the part of wisdom to use single agents wherever possible.

Supportive Treatment

Regardless of the proved therapeutic value of the sulfonamides and antibiotics in bacterial pneumonia, they are not to be used to the exclusion or neglect of established supportive measures. The pneumonia patient requires competent nursing care, complete mental and physical rest, sufficient fresh air, easily

digested food, and adequate bowel elimination. Morphine is still a valuable aid in the control of certain disturbing features of this disease, such as apprehension, restlessness and pain; but it should be used in small doses, and should be employed with special caution in hypoxemic patients.

Fortunately, the severity of abdominal distention is less pronounced in pneumonia patients receiving chemotherapy than was formerly observed, although occasional patients will require enemas, rectal tubes, local heat to the abdomen, and drugs such as solution of posterior pituitary. It is best to avoid the employment of cathartics. Digitalis should be administered when indicated, but not as a routine procedure.

Special emphasis must be given the nourishment of patients with pneumonia. In many patients failing to respond adequately, and especially those in older age groups, the need is not so much for additional chemotherapy as for nutritional supplementation. It is necessary to ensure that an adequate diet is supplied, and it is equally necessary to make sure that it is ingested. Tube feeding and parenteral infusions must be utilized if adequate intake cannot be ingested.

Oxygen therapy is a useful adjuvant in all seriously ill pneumonia patients. Cyanosis is an inaccurate indication of hypoxemia, and the wider availability of arterial oxygen saturation determinations is essential if oxygen therapy is to be intelligently administered.

Management of Complications

A search for complications should be made in every patient with bacterial pneumonia who does not respond promptly to chemotherapy. Most frequent are pleural complications.

Pleural effusions—Small asymptomatic pleural effusions are common accompaniments of pneumonia but scarcely deserve the title of complications, since treatment is not required. Moderate-sized or massive pleural effusions occur not infrequently. In the majority of instances of bacterial pneumonia these effusions are responsible for few symptoms so long as antibiotic therapy is continued. Aspiration usually reveals a clear or only slightly cloudy fluid which is sterile on culture. Large sterile exudates of this type were not encountered prior to the development of chemotherapy and they may be properly considered a new entity, best designated as the sterile postpneumatic effusion. Many such effusions, particularly those of moderate size, will resorb without local therapy under continued systemic administration of antibiotics. The larger effusions present a more serious problem. So long as systemic antibiotic therapy is continued, the effusion remains sterile on culture and the patient remains afebrile, but after the termination of antibiotic treatment, symptoms develop and aspiration may then reveal frankly purulent fluid. In patients with persistent large sterile effusions, which recur after repeated needle aspirations, it may be assumed that the pleural space cannot be obliterated by expansion of the lung because the lung has become incarcerated in a fibrinous envelope. Treatment under these circumstances should consist of either surgical decortication or the use of streptococcic enzymatic debridement.[10]

The management of frankly purulent effusions or empyema has been revolutionized during the last decade by the introduction of penicillin, streptodornase and surgical decortication. There is no longer a place for tube or open drainage in the treatment of empyema. A majority of empyemas can be successfully treated medically by daily aspiration and instillation of 50,000 units of penicillin in addition to high level systemic penicillin therapy. If the aspirations are performed skillfully and regularly, re-expansion of the lung can usually be secured without loculation. If, despite instillation of penicillin, the lung fails to re-expand because of fibrin deposits, enzymatic decortication by use of streptodornase should be attempted. If all efforts at medical therapy are unsuccessful, surgical intervention is required. It should be emphasized that the role of surgery is not, as in the past, to control infection by drainage. Control of infection is as a rule effected by antibiotic therapy and surgery is required only to decorticate the lung in order to permit obliteration of the pleural space.

Abscess of the lung—The need for surgical drainage of pulmonary abscesses is equally rare at present. Systemic antibiotic therapy employing neo-penil and/or the other antibiotics in high dosage will control most abscesses complicating pneumonia. Occasionally, intracavitary instillation of antibiotics may be attempted in large abscesses which are readily accessible to needle aspiration. If these methods fail to secure closure of the abscess cavity, thoracotomy and pulmonary resection may be carried out with greater safety and better preservation of pulmonary function than could have been achieved by surgical drainage. A word of warning is in order, however, concerning the medical treatment of pulmonary abscess. We have treated several patients with large pulmonary abscesses and have obtained by prolonged systemic penicillin therapy complete resolution of the inflammatory process so that the ordinary roentgenogram appeared normal. Use of planigrams and bronchograms, however, revealed residual cavities. This finding presumably accounts for the considerable frequency of relapse after apparent medical cure of pulmonary abscess.

Meningitis—Meningitis is now a relatively uncommon complication of pneumonia. Lumbar puncture is indicated whenever neurologic signs suggest possible meningeal irritation, but in most instances frank meningitis will not be found. Treatment of pneumococcal, streptococcal or staphylococcal meningitis involves the thorny problem of intrathecal penicillin administration. Although theoretically adequate spinal fluid levels of penicillin can be obtained by administration of very large doses intravenously or intramuscularly, the mortality rate in these forms of meningitis remains high. Many experienced investigators still employ intrathecal penicillin in such cases on the basis that the benefit derived far outweighs the danger of neurologic complications resulting from intrathecal therapy.

Acute bacterial endocarditis—Acute bacterial endocarditis complicating pneumonia can readily be controlled by adequate doses of antibiotics if the presence of this complication is recognized before extensive valvular damage occurs. Chemotherapy should be continued for at least four weeks.

Purulent pericarditis—Purulent pericarditis should be treated by local instillation of penicillin as well as by systemic administration in high dosage. Attention has recently been called to the characteristic electrocardiographic pattern of pneumococcal pericarditis. Recognition of the pattern of extremely high ST segments should facilitate the diagnosis of this complication.

Retarded or incomplete resolution of a pneumonia—Retarded or incomplete resolution, as indicated by serial roentgenograms, is a troublesome and not uncommon complication. Such behavior must immediately arouse the suspicion of an error in diagnosis. Thorough study is indicated to eliminate the possibility of neoplasm, tuberculosis and other subacute or chronic lesions that may produce or simulate pneumonia. Bronchoscopy and planigraphy must be performed before one can safely consider a residual lesion an instance of unresolved pneumonia.

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Observations on Some of the Basic Concepts of Electrocardiography

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Most electrocardiographers do not appear to understand that certain concepts, widely accepted and regarded as basic, are derived from simplifications of a type more familiar to engineers than to physicians. Consequently beginners are taught technics, the validity of which depends on the applicability of these simplifications to the conditions encountered in the body. An attempt has been made to inquire into a few of these matters as simply as possible.

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During the past 10 years the practice of clinical electrocardiography has spread rapidly beyond the group of physicians with a special interest in cardiology. Not only internists but also many general practitioners have adopted the procedure for reasons such as the following: (1) Small portable paper-writing machines have become available eliminating the need for a darkroom and the nuisance of developing pictures. (2) The fidelity of the new machines is usually good enough for ordinary clinical purposes, but constant vigilance concerning performance is still highly desirable. (3) The laity has become so sophisticated that a "cardiogram" is regarded as an essential part of the examination of the heart. Thus, without the test, a physician's opinion may lack the prestige and authority needed for adequate management of his patient. (4) Although the sphere of usefulness of electrocardiography may be considerably different from what the laity conceive it to be, its importance as a diagnostic measure in most types of heart disease has been well established. The need for its use in so-called health examinations is beginning to be understood. (5) The diligent physician finds that electrocardiography, in appropriate cases, helps to sharpen his clinical acumen.

Some experts shudder at the thought that physicians, either self educated in electrocardiography or, at most, graduates of the standard four week courses, should interpret tracings. Neophytes who grossly overestimate their abilities are not incapable of mistakes. However, the normally cautious beginner can almost always avoid serious error by calling for help when he is in doubt. If he applies himself seriously, his need for help rapidly diminishes. In any event the veterans of electrocardiography cannot stop the movement, and because electrocardiography tends to increase the efficiency of physicians, its use should be encouraged.

This article is directed not to the experts on electrocardiography but rather to the host of physicians who have become interested in the subject with only a limited amount of time to devote to its study. The beginner in electrocardiography can learn much regarding its practical aspects by examining tracings with

the aid of some of the excellent books on interpretation now available. However, I know of no literature which will furnish a clear account of the basic concepts underlying electrocardiography. Although it is beyond my ability to elucidate these matters, partly at least because of large gaps in our knowledge, I hope that a discussion of some of them will indicate that what has been called "modern electrocardiographic theory" is far from settled and that much of what is being almost universally taught may have to be discarded. If so, this will mean that various technics, the merits of which depend solely on the validity of currently accepted theory, must be reviewed. Thus the subject is one of considerable practical as well as theoretical interest. I shall consider mainly the impacts of recent work.

Newer views of ion migration during depolarization and repolarization and their significance—The unit of electrical activity responsible for the electrocardiogram occurs in the individual myocardial fiber. These unit electrical changes during excitation and recovery, the building blocks of electrocardiography, are of first-rate importance.

For a long time it has been taught that when excitation occurs, the cell membrane becomes permeable and potassium ions migrate from inside the cell to the outside and remain there until the end of the excitatory period, whereupon they return to the inside. Because potassium is a cation but relatively negative to sodium, its concentration along the outside of the cell membrane was supposed to cause the fall in action potential characteristic of the beginning of excitation. The potential was then supposed to remain constant until the end of the excitatory period when in connection with the return trip of the potassium ions to the inside, potential at the outer surface of the cell membrane again rose to the preexcitatory or resting level.

The abovementioned cell membrane theory was widely accepted for many years. Writers on electrocardiography have tried to reconcile their findings with it, and this attempt has led to some remarkable logical gymnastics. The idea of the ventricular gradient, which has been and still is accepted in many quarters as a valuable contribution to electrocardiography, is based on that theory.

It now appears that the classic cell membrane theory does not offer a satisfactory explanation of electrical changes.[1] We are informed that permeability of the cell membrane is selective and the initial fall in potential at the outer surface is associated with migration of sodium ions to the inside. This is followed immediately by migration of potassium ions to the outside with restoration of potential at the surface practically to its original level. Not much is known at present regarding the rate of the return trips of sodium and potassium ions to their "resting" state although the RS-T segment and the T and U waves are probably landmarks of such events. These matters will doubtless be determined in due time. A fascinating new field of investigation has been opened which is bound to lead to further results of great value to electrocardiography. One of these should be retirement of the barren concept of the ventricular gradient which has been so greatly admired in certain quarters but which could not possibly further our knowledge. It will probably be far more useful to try to account for electrocardiographic changes on the ionic basis of electrical activity.

The Einthoven equilateral triangle hypothesis—In the early 1930's interest in the detection and localization of ventricular lesions led to question as to the adequacy of Einthoven's limb leads. It was this question that led Wood and me[2,3] to the use of chest leads to detect experimental and clinical myocardial lesions due to coronary obstruction. The use of chest leads immediately raised new problems, including methods of pairing electrodes. The late F. N. Wilson conceived the idea that in chest leads an exploring electrode should be paired with an electrode with minimal potential variation.[4] He was able to show that if the assumptions which Einthoven made to support his equilateral triangle hypothesis were valid, the sum of the potential variations of cardiac origin transmitted to the right arm, left arm and left leg equals zero. Thus it became a relatively simple matter to construct a central terminal which, when con-

nected with the right arm, left arm and left leg with appropriate resistance interposed and paired with the exploring electrode, yielded "unipolar" electrocardiograms presumably corresponding to the potential variations transmitted to the exploring electrode.

Wilson was aware of at least most of the assumptions he had to make, realized that some of them were open to attack and, in contrast with Einthoven, made considerable effort to support them. He appears to have been convinced that the error involved in his unipolar procedure is not great enough to be of practical importance. One may agree that it is not of great practical importance, so far as precordial leads are concerned. The results differ so little from those recorded in CR leads that an advocate of one as against the other procedure would have considerable difficulty in proving his point. The trouble arises when unipolar leads are made at positions further from the heart than the precordium, such as the left leg. This lead shows considerably more than a negligible difference from lead 2; we now obtain a pattern of deflections which are an algebraic mean of leads 2 and 3. Does this synthesis possess some special significance or is it merely a jumble of potentials which tends to obscure rather than reveal myocardial changes?

The line of cleavage of opinion in electrocardiography at present is between (1) those who believe that differences in potential of cardiac origin that develop on body surfaces can be accounted for by the simple theory of Einthoven or, as in the case of certain applications of spatial vectorcardiography, by some almost equally simple modification of it, and (2) those who regard the electrical field of the heart as so complex that (a) unipolar leads probably possess no special merit but may be inferior to other leads and (b) spatial vectorcardiography as now practiced, although perhaps an entertaining pastime, possesses no other virtue. The advocates of the schematized procedures have frequently pointed with pride to their achievements. Their opponents could claim that, had they not forsaken simple procedures, they might have accomplished considerably more. For example, it could be contended that the greatest achievement of the late F. N. Wilson was his classic work on bundle branch block which was done with CF leads.[5]

About 10 years ago I concluded that it was fruitless to argue whether unipolar leads constitute a great advance or a disaster on the basis of the data we possessed, and that it seemed necessary to bring electrical engineers and biophysicists at least to the edge of the fray to supply quantitative data of various kinds. Considerable progress has since been made along such lines. In the near future we may expect abundant data on measurements of conductivity of tissues and studies on effects of eccentricity of current dipoles within solid bodies on differences of potential between various parts of surfaces. Schwan and his colleagues[6] have questioned the significance of conductivity measurements of Kaufman and Johnston[7] and appear to have obtained differences so great among blood, fat, solid organs, lungs and bone that they raise considerable doubt regarding the applicability of Einthoven's assumption of homogeneous conduction. Those of us unfamiliar with the possible concealed pitfalls of technics devised to measure conductivity of living tissues *in situ* must await the consensus of competent biophysicists before we prejudice ourselves in favor of one set of data rather than another.

In the past, Einthoven's assumption that the heart may be considered an electrical point at the center of an equilateral triangle, although recognized to be a rough approximation, has not generally been regarded as a serious objection to his hypothesis. Wiggers[8] has reminded electrocardiographers disposed to object to this assumption that Einthoven's attainments in physics and mathematics were superior. Despite this potent argument, which should probably quell all but the most rash, it might not be amiss to remember that not only is the heart eccentrically placed but also, by virtue of the manner in which it is activated, the point bisecting the vector line may conceivably undergo considerable migration during the inscription of the QRS complex.

Ernest Frank of the Electro-Medical Section of the Moore School of Electrical En-

gineering has recently concluded on the basis of mathematical study that in the case of a sphere composed of a homogeneous conductor with a current dipole placed exactly at the center, the potentials of three points on the circumference defining an equilateral triangle would be in accord with Einthoven's hypothesis. However, relatively slight eccentricity of the current dipole introduced considerable discrepancy in results. Frank's calculations appear to have been confirmed by the locations of iso-potential lines on a hemispheric model.[9] This is an unexpectedly severe blow to Einthoven's hypothesis from a quarter in which it had not been under serious attack. Experimental studies are urgently required in a body shaped like the human trunk with the current dipole placed in a position corresponding to the usual position of the heart. Frank and Kay,[10] the latter a member of the staff of the Robinette Foundation, are now carrying on such studies with the aid of a device constructed by Frank, by which the potential of the reference electrode is presumably maintained in correspondence with the mid-potential of the current dipole.

The ultimate decisions in electrocardiographic theory should not be left entirely in the hands of biophysicists and engineers, no matter how valuable the data they elicit. They can probably tell us after adequate study whether the errors inherent in simplifying assumptions such as those of Einthoven are so great that such assumptions should be abandoned. If, however, they fail to find such errors, we are not relieved of the necessity of making the final decisions ourselves. At present the following points are perfectly clear.

1. Lesions located in certain parts of the heart are well reflected in electrocardiograms and lesions of equal size in other parts of the heart are poorly reflected.

2. Certain lesions are capable of producing marked changes in some precordial leads without any appreciable changes in other precordial leads or in limb leads.

3. Lesions on the posterior wall of the left ventricle may produce marked changes in leads 2 and 3 without observable change in lead 1.

4. Unless we assume far better conductivity of blood than solid tissues, the electrocardiographic findings produced by lesions involving the endocardial aspects of the left ventricle become difficult to explain.

5. The marked reduction of potential differences on body surfaces when pericardial effusion occurs suggests "short-circuiting" of currents.

6. Body surface potential differences are disturbed comparatively little by pneumothorax, including the surface which is directly over the air.

7. By using the right upper part of the back as a reference point, the number of variations in electrocardiographic patterns is greatly reduced.

8. By pairing electrodes across the attachments of upper extremities, the pattern of potential differences on either side resembles that obtained by using the right upper part of the back as a reference point with the exploring electrode on the appropriate arm and does not resemble the unipolar arm potentials.

9. Differences of potentials between points on the lower part of the body tend to be much smaller than those between points on the upper part of the body, suggesting that resistances are much less on the lower part.

10. Positions at which maximum changes in QRS complexes and T waves occur caused by a lesion may not be identical, possibly because of movements of the heart.

Until these relationships and possibly others are adequately accounted for by electrocardiographic theory, soundly based on principles of physics, we have little reason to feel complacent regarding the scientific basis of electrocardiography. At present it seems possible and even probable that the combination of inhomogeneity of conduction, departure from the spheric in the shape of the trunk and eccentricity in position of the heart, especially the left ventricle, is of major importance in determining the characteristics of electrocardiograms. If so, the old concept of favored routes of conduction between parts of the heart and parts of the body surface which seemed essential to account for relationships observed by Livezey, Wood and

me[11] will require reinvestigation. It will be interesting to observe if or when unipolar electrocardiography and spatial vectorcardiography, as now practiced, suffer the fate which has already overtaken the ventricular gradient.

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Heart model with cut-away sections to show right auricle and right ventricle.

(Wide World photo)

The Cultivation of Poliomyelitis Virus in Tissue Culture of the Human Uterus with Emphasis on the Broader Aspects

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A historical background of the application of tissue culture technics to the laboratory study of poliomyelitis viruses is given. Tissue cultures are defined briefly and the two types usually applied to poliomyelitis virus studies described. Uses of the technics are outlined and further possible applications in poliomyelitis research suggested.

THE work of Enders, Weller and Robbins[1-4] opened a new epoch in poliomyelitis research. Using their methods, it became possible to cultivate the poliomyelitis virus in test tubes or flasks rather than in monkeys or mice. This new laboratory tool makes possible many experiments which were impossible or impractical to perform by older methods of animal experimentation. By application and development of this tool the ultimate control of poliomyelitis will be brought nearer. However, one of the greatest contributions of tissue culture approach may well be the dramatic impact with which it demonstrates that polio viruses grow very well in many tissues of non-nervous origin.

Before describing these methods in greater detail it is well to point out that tissue cultures have been used in the laboratory for many years. A tissue culture consists of certain tissue cells supported and nourished in vitro in such a manner that they grow. For example, a culture of pure epithelial cells may be obtained by suspending a thin slice of rabbit cornea in a plasma clot on a cover slip; or a culture of fibroblasts can easily be obtained from a small piece of lung, liver, spleen or heart suspended in a suitable medium. Parenchymatous cells are much more difficult to propagate, but this too can be accomplished, especially if embryonic tissues are employed. Tissue fragments suspended in a liquid medium are useful for some purposes, but in this type of tissue culture outgrowth of new cells does not occur because there is no framework to support new growth of delicate filaments.

In tissue cultures, viruses may find conditions suitable for multiplication. Certain viruses which give rise to well recognized intracellular inclusion bodies in the infected host cell have been intensively studied in tissue culture. Step-by-step changes in the host cell have been observed and correlated with the production of virus and the development of the inclusion body. Vaccinia, herpes simplex and psittacosis have been studied in this way. All produce prompt and dramatic changes in the tissue culture cells.

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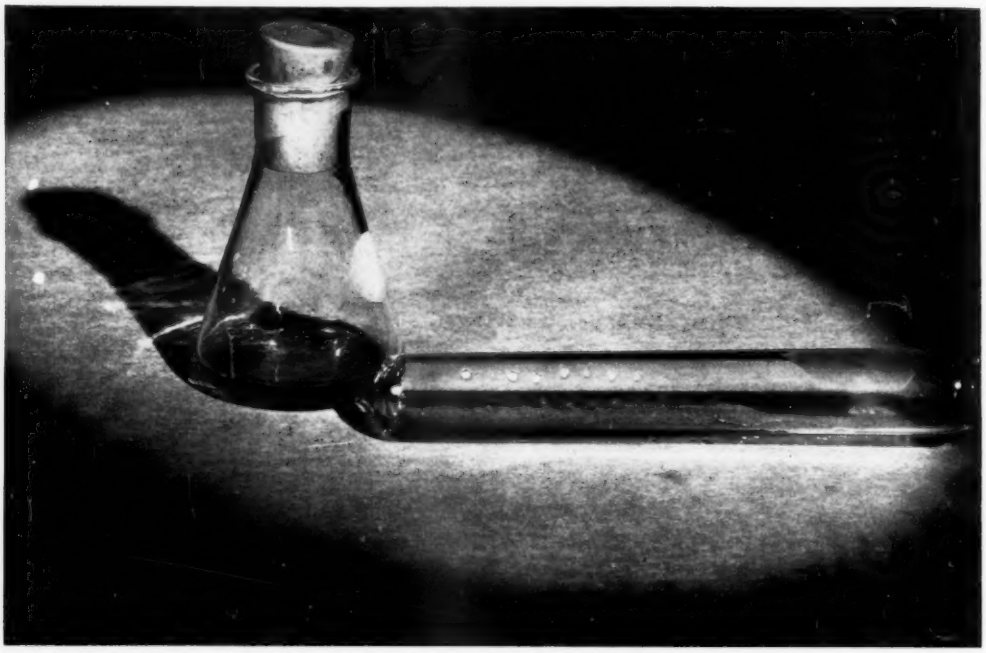
FIGURE 1. Erlenmeyer flask culture *(left)*; roller tube culture *(right)*.



It would appear strange if cultivation of poliomyelitis virus in tissue cultures had not been tried years ago, and indeed it has been attempted many times in the past. All attempts before those of Enders, Weller and Robbins led to disappointment, no changes being observed in the tissue culture cells and no increase in virus detected by injecting the supernatant fluid into suitable laboratory animals. In contrast to these negative and largely unpublished results, Enders, Weller and Robbins noted that poliomyelitis virus could be successfully propagated on human embryonic skin and muscle, foreskin,[2] mature kidney, and uterus.[3] Their success can be attributed to (1) holding their cultures many days longer than was the usual custom in propagation of other viruses in tissue culture, (2) keen observation of minute changes in the *p*H of the medium and histology of the tissue fragments, (3) selection of human tissue for their tissue cultures and (4) painstaking repetition of experiments until proof was established. Since the original report, it has been found that all polio viruses can be grown in a variety of human and monkey tissues. Various modifications of the original technics have been used for production of cell-free virus, neutralization tests, typing of viruses and even direct isolation from human material.

The technics of tissue culture are relatively simple to describe, but require extreme care and attention to details. At present they are not practical for use in a routine hospital diagnostic laboratory, but are available in most sections of the country in special research laboratories.

Materials and Methods

A full description of the materials and methods may be found in the bibliography, but briefly the two major methods in use in this laboratory are as follows:

1. *Erlenmeyer flask method*—Tissue fragments minced with scissors to 1 to 2 mm. in diameter are introduced into a 25 ml. Erlenmeyer flask in sufficient quantity to cover the bottom in a single layer. Three milliliters of a nutrient medium consisting of 3 parts Hanks balanced salt solution and 1 part Simms ultra-

FIGURE 2. Uninfected explant of human uterus showing proliferating fibroblasts (x 140).

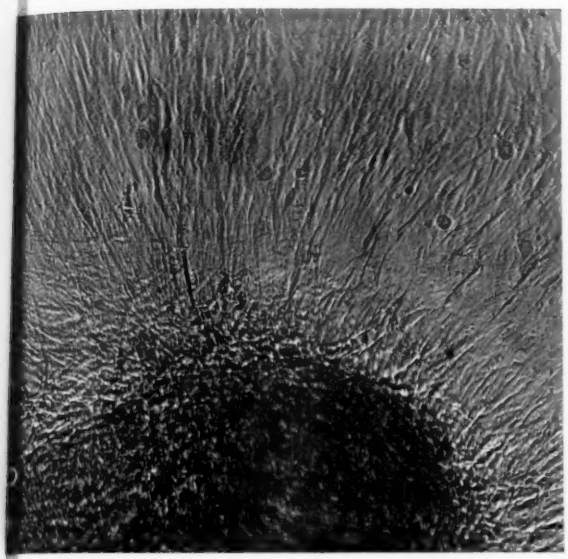
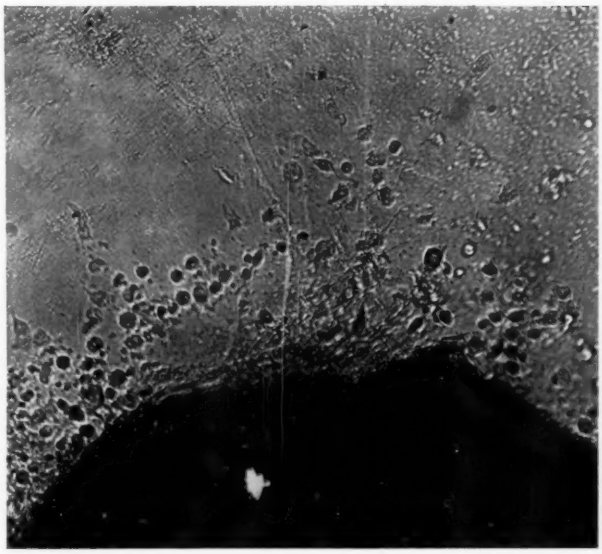


FIGURE 3. Explant following infection with poliomyelitis virus.



filtrate of ox serum with phenol red indicator are introduced. The cultures are incubated at 35° C. and the supernatant fluid changed every three to four days. (Figure 1.)

2. *Roller tube method*—Six to ten tissue fragments 1 to 2 mm. in diameter are clotted to the side of the lower half of a test tube by means of chicken plasma and chick embryo extract (to supply thromboplastin). One milliliter of nutrient medium is added, consisting of Hanks-Simms medium with added growth-stimulating horse serum and beef or chicken embryo extract. The tubes are placed in a roller drum with a 10 degree slant from the horizontal and rotated at six revolutions per hour. They are incubated at 35° C. The supernatant nutrient medium is changed every three to four days. The tissue fragments, or explants, are observed through the side of the test tube under the low power of the microscope. Within 8 to 12 days a halo of fusiform fibroblasts is noted to migrate from and surround the explant. (Figures 1 and 2.)

Evidence of virus infection of tissue cultures—Enders, Weller and Robbins noted two important changes in the tissue cultures infected with poliomyelitis virus.[4] The first was a metabolic one and was observable grossly in the color change of the indicator in the nutrient medium. Uninfected tissue cultures slowly metabolize the glucose in the nutrient medium and the resulting acid end products change the phenol red indicator from red to yellow. Infected tissue cultures metabolize more slowly and the nutrient medium tends to remain an alkaline pink. This reaction of virus growth was most useful in the flask cultures. The second and most important evidence of polio virus in a tissue culture is the direct observation of changes in the tissue cells infected with poliomyelitis virus. Uninfected tissues in roller tubes have the aforementioned halo of clear fusiform fibroblasts surrounding each explant. (Figure 2.) Following infection with the virus, the migration of the fibrocytes ceases and in 4 to 16 days degenerative changes appear in the individual fibrocytes. These changes consist of loss of the spindle shape of individual fibrocytes and a "rounding up" of the cell to a globular form

TABLE 1

USES OF TISSUE CULTURE IN LABORATORY STUDIES OF POLIOMYELITIS VIRUS

1. Isolation of virus from stool, nasopharyngeal secretions, blood and other possible sources
2. Titration of virus
3. Typing of virus by means of neutralization tests
4. Antibody determination and titration
5. Antigen production for vaccine and complement fixation tests

with refractile granular cytoplasm. This is followed by lysis of the cytoplasm and pyknosis of the nucleus. These cytopathogenic changes, especially the refractile globular appearance of cells of infected cultures, are quite typical and with experience may be readily differentiated from the nonspecific deterioration which occurs in aging cultures. (Figure 3.)

Modification of basic methods—Following the demonstration by Enders that poliomyelitis virus could be propagated in non-neural tissues, other workers made additional contributions to laboratory cultivation of poliomyelitis viruses. Smith, Chambers and Evans[5] observed that the virus would multiply in Erlenmeyer flask cultures of human adult testicle. Later they observed that it also could be propagated in flask cultures of monkey testicle.[6] The use of monkey testicle was also reported by Syverton, Scherer and Butorac,[7] Ledinko, Riordon and Melnick,[8] and Youngner, Ward and Salk.[9] For these workers monkey testicle provided a more constantly reliable source of tissue than human tissues, and when used in the roller tube technic provided clearly observable cytopathogenic changes when infected with virus.

In our laboratory human uterus has been utilized most extensively because of a constant supply. There are certain theoretical and practical advantages in using human tissue for the isolation and study of a strictly human pathogen and uterus provides clear cytopathogenic changes.

Uses of tissue culture in laboratory studies of the poliomyelitis virus—The workers already named, as well as Enders and his coworkers, rapidly applied the two tissue culture technics to a number of uses.

1. *Isolation of poliomyelitis virus from the stool*—Using antibiotics to afford bacterial sterility, stool suspensions may be introduced directly into tissue cultures. Twenty per cent suspensions of stool specimens are made in distilled water. Penicillin and streptomycin are added to a final concentration of 500 units and 500 mcg. per milliliter respectively; 0.1 ml. of this material may then be inoculated directly into a roller tube. Several serial passages of the tissue culture supernatant liquid into fresh tissue culture tubes usually are made to adapt the virus to the tissue culture system and to dilute out any nonspecific cytotoxic effects of the stool.

This method of isolation of poliomyelitis virus from stool may in the future be applied to nasopharyngeal secretions, blood, flies, sewage and other sources difficult to study before the advent of tissue culture technics.

2. *Titration of virus*—To determine the amount of virus in any suspension, stool or throat washing, tenfold dilutions are made in Hanks balanced salt solution and 0.1 ml. of each dilution (10^0 to 10^4) is added to each of three new roller culture tubes which have the usual proliferating explants. The cytopathogenic changes are looked for to determine the presence of virus in each of the dilutions. In this way, the titer of virus in the original inoculum may be determined.

3. *Typing of virus by neutralization tests*—Following isolation and titration of a virus from stool an attempt can be made to determine the type of the isolated virus—that is, whether it is similar to serologic type I (Brunhilde), type II (Lansing), or type III (Leon). To 100 tissue culture doses of the unknown virus is added specific antiserum for type I virus. The mixture is then kept at 4° C. for two hours, after which it is inoculated into roller tube cultures and incubated at 35° C. as previously described. This is repeated with each of the other two specific types of antiserum. The unknown virus will be neutralized by its homologous type antiserum and in tubes inoculated with this mixture the tissue culture cells will continue to grow and pro-

liferate, while in tubes inoculated with unknown virus plus the other two types of antiserum the tissue culture cells will show cytopathogenic changes.

4. *Antibody determination and titration*—Tissue culture technics can be used to determine the presence of specific poliomyelitis neutralizing antibody in serum and also to titrate this antibody. Serum may be mixed with each of the three known polio viruses and its ability to neutralize the viruses determined by injecting the mixture into a fresh tissue culture tube.

If the serum can prevent cytopathogenic change when mixed with a virus it is considered to contain specific neutralizing antibodies for that type virus. To determine the titer of this antibody the serum may be serially diluted, mixed with specific virus and the end point noted where neutralization stops and cytopathogenic effects occur. Using these methods the serums of various human and animal population groups may be screened for the presence of neutralizing antibodies for all three types of poliomyelitis virus.

5. *Virus production for vaccine or complement-fixation antigen*—Flask cultures afford an excellent means for the large scale production of virus as demonstrated by Svedmyr, Enders and Holloway.[10] They produced large amounts of each type virus in a modified flask technic for use as complement-fixing antigens. Using the same method it would be possible, when desired, to produce types I, II, and III poliomyelitis virus for use in a vaccine of known ingredients and of non-nervous tissue origin.

Future Problems for Poliomyelitis Research

Tissue culture technics have reduced the cost and increased the speed of poliomyelitis research. By applying the technics to problems which would have been quite costly and protracted using laboratory animals, new studies may be undertaken. Epidemiologic surveys to isolate viruses from stool and to study antibody response of cases and family contacts is being done in this laboratory. Titration of stools and nasopharyngeal secretions of poliomyelitis patients on successive days; longitudinal studies in newborns throughout infancy for stool virus and antibodies; antibody surveys of the animal kingdom; search for virus in the household on toys, utensils, uncooked food and water, and further studies on viremia are all projects now within the realm of this technic.

Summary

1. The historical background work of Enders, Weller and Robbins in growing poliomyelitis virus in tissue cultures is presented.

2. The technics are briefly presented.

3. New modifications of the basic technic by other workers are described.

4. Specific uses of tissue cultures in polio research are outlined.

5. Further possible applications of the technic in polio research are described.

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Therapeutic Application of Ultrasonic Therapy

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Since it has been shown that ultrasonic radiation has therapeutic possibilities, this form of energy has been extensively employed in medicine. It has found its chief value in the treatment of the arthritides and allied rheumatoid disorders and in diseases of the peripheral nerves and blood vessels. Ultrasonic energy can produce irreversible destructive changes. Therefore it must be applied with care, in proper dosage, and by experienced personnel. Ultrasonic radiation is local therapy capable of producing analgesic effects without influencing underlying causes.

GEORGE MORRIS PIERSOL

INTEREST in the biologic responses induced by the application of ultrasonic energy dates from the observations of Wood and Loomis[1] in 1927 on "physical and biologic effects of high frequency sound waves of great intensity." It was 1939 before ultrasonic therapy was developed and suitable apparatus devised to carry out such treatment. The interest in this centered chiefly in Europe, notably in Germany and Austria, until interrupted by World War II. Since the war widespread interest in the diagnostic and therapeutic possibilities of ultrasonic therapy has developed, especially in England and on the continent of Europe, where this form of treatment has been used extensively.

Until recently the American medical profession has paid little attention to this field. During the last few years, however, an increasing number of physiatrists in this country have employed this type of therapy. Furthermore, groups of American investigators are now concerned with various biophysical problems involved when human tissue is subjected to ultrasonic energy. The use of ultrasound waves is an important addition to the technics of physical therapy, and promises to become a valuable therapeutic and diagnostic procedure. It is timely, therefore, for physicians to familiarize themselves with this form of treatment and to learn its possibilities, its limitations and its dangers.

Equipment

The human ear is unable to perceive sound waves that vibrate at a frequency of more than 20,000 vibrations per second. Vibrations of a higher frequency, which are inaudible to the human ear, are referred to as ultrasonic waves. Sound waves of a frequency of 1,000,000 vibrations per second (1 megacycle) have been found most generally useful thera-

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peutically. Experimental evidence indicates that deep penetration of heat cannot be obtained at frequencies much less than 1 megacycle. Medical ultrasonic equipment has been developed which can satisfactorily generate sound waves of such a frequency.

Equipment designed for the medical application of ultrasonic energy is composed of a high frequency generator and an ultrasonic transmitter. The generator produces an electric current of the desired frequency (1,000,000 oscillations per second). The high frequency electric current brings about, in a specially constructed quartz crystal, synchronous vibrations which generate sound waves. Certain materials, notably quartz and ceramics, are referred to as "piezo-electric" because they develop mechanical vibrations when opposite sides of the crystal are subjected to alternating electric fields. In apparatus designed for the employment of ultrasonic energy therapeutically the piezo-electric crystal and its electrodes are enclosed in a light metal case. This unit is called a transducer or "sound head." It is this portion of the equipment that is employed in treatment. The transducer is so constructed that the ultrasound waves are emitted only from the transmission plate or face of the treating head. It is in the transducer that electrical oscillations are converted into mechanical vibrations which in turn produce sound waves.

In order to transmit ultrasonic energy effectively, the face of the transducer must be pressed against the area of the body to be treated. Since ultrasonic radiations cannot pass through a vacuum but require for their propagation a material medium, an air-free contact must be established between transducer and tissue. This is accomplished by using a suitable conducting coupling medium, such as special ointments, liquid petrolatum or water. When water coupling is employed, both the subject and the transducer are immersed. Sound waves travel approximately up to 20 times faster in solids and four times faster in liquid than they do in air.

Properties of Sound Waves

Schwan and Carstensen[2] state that sound waves, whether propagated in air at audible frequencies or in body tissue at high frequencies, bring about a disturbance that consists of alternate condensations and rarefaction within the medium. The condensations travel at a velocity characteristic of the properties of the medium. The transmission properties of a given medium are determined by its acoustic impedance. If the magnitude of the acoustic impedance of water is taken as a base, it is found that muscle, fat and glandular tissue all have impedances of magnitudes within 15 per cent of that of water; the impedance of a quartz piezo-electric crystal is nearly 10 times that of water, whereas the impedance of air is less than 1/1000 that of water. As the sound wave travels through the medium a definite fraction of the energy of motion is transformed into heat in each unit of distance.

In their admirable review of ultrasonics in medicine, Nelson, Herrick and Krusen[3] state that because of their short wave length, ultrasonic waves exhibit some unique properties. They are completely reflected at the interface between two mediums if the critical angle is exceeded, travel in straight lines, exhibit interference phenomena, and are refracted. These authors emphasize the tremendous forces that are developed during the propagation of ultrasonic waves. Their observations show that a particle in the field is forced to vibrate through 800,000 cycles per second, yet it is not displaced from its position of rest by more than 0.00001 cm.

Effects of Ultrasonic Radiation

Those who are employing ultrasonic energy in the diagnosis and treatment of disease in man are chiefly concerned with the effects of ultrasonic radiation. This aspect of the subject is well considered by Schwan and Carstensen.[2] They state that the ultimate biologic effects of high frequency sound waves on tissue must necessarily be based on primary physical processes that are caused by ultrasound in living matter. They consider (1) the thermal effects, the importance of which in therapeutic and biophysical problems has been well established, and (2) a number of

known nonthermal effects which may or may not play a significant role in treatment.

Schwan and Carstensen state that the generation of heat in tissue by ultrasonic energy may take place throughout the volume of the tissue. This phenomenon they refer to as "volume" heating. Volume heating is a characteristic of completely homogeneous fluids and solids. The second way in which heating of tissue occurs is more complicated, because of the presence of abrupt interfaces found in many tissues and tissue aggregates. This phenomenon they term "structural" heating. Such localized heating will occur when ultrasonic rays are impeded at the interfaces present in complicated tissues, as those which exist between bone and muscle and muscle and tendon.

In structural heating, losses are brought about by scattering, by multiple reflections and by the generation at the interface of what are known as shear waves. The rapid decay of these waves produces localized heating in the region of the interface. For example, Nelson, Herrick and Krusen[3] reported temperature rises in the bones of living dogs that were five times the rise in surrounding tissue. This is an example of the structural heating that may occur at interfaces. Selective temperature rises also have been observed in macroscopic membranes. In volume absorption, however, the heat production is more uniform.

Because of the excessive localized heating at interfaces that may occur from ultrasonic radiation, it is of importance from the medical standpoint to understand the distinction between these two types of heating. In order to avoid possible irreversible destructive changes, care must be exercised to see that sound intensity at an interface such as bone is maintained at a safe level.

Nonthermal effects which may or may not be of therapeutic significance are classified by Schwan and Carstensen as follows:

1. *Increase of membrane permeability*—There is evidence that the permeability of a macroscopic membrane under ultrasonic radiation is increased beyond that which can be explained on the basis of the heating of the membrane.

2. *Resonance effects*—Gas bubbles in liquid oscillate radially when subjected to a sound field. The destruction of red blood cells and microscopic animals by resonant gas bubbles in the sound field have been observed. The phenomenon is explained on the basis of complex oscillations of the cells.

3. *High intensities*—High intensities of sound may produce changes of state in the medium by the formation of gaseous cavities (cavitation) or by breaking long-chain molecules (depolymerization).

The part played by the several known effects of ultrasonic radiation in the treatment of disease in humans is still a matter of discussion. At present the majority of American investigators are inclined to the opinion that the thermal effects are chiefly responsible for the therapeutic results claimed. There are others, particularly in Europe and in England, as well as some observers in this country, who insist that the clinical improvement observed after ultrasonic therapy cannot be explained on the basis of thermal effects alone. These workers maintain that mechanical, chemical and biologic effects are equally important. Although it is generally agreed that ultrasonic energy can produce these effects, it must be admitted that at present they are poorly understood, especially as to their influence on the human organism. Buchtala[4] in a discussion of this subject states that our earlier views concerning the action of ultrasonic therapy must be modified. At first only the thermal and mechanical effects were considered significant; now it is realized that physiochemical and highly specific neurotrophic effects are important elements in the biologic action of ultrasonics. On the other hand, Schwan[2] believes that it is certain that ultrasonic radiation produces heat in the body tissues; however, whether purely mechanical or other nonthermal effects play a significant role in treatment has not been determined.

A limited personal clinical experience leads to the conclusion that such symptomatic relief as has been obtained from ultrasonic treatment is attributable to the heat produced. Further investigations must be undertaken and many more controlled clinical observa-

tions recorded before we arrive at a satisfactory evaluation of this aspect of ultrasonic therapy.

Dangers

Every active therapeutic agent capable of doing good when properly used has harmful potentialities when employed unwisely. Ultrasonic therapy is capable of inducing destructive changes in tissue when indiscriminately and carelessly used. This has been shown by several investigators, notably the group at the Mayo Clinic, whose experimental studies have thrown much light on problems connected with ultrasonic therapy.[5] For the most part they used maximal dosage, greater in proportion to the size of their experimental animals than the doses ordinarily employed in the treatment of patients. Nevertheless they showed that the ultrasonic machines commonly used in medicine if employed at maximal dosage can severely damage many types of tissue. They found that ultrasonic radiation produced sharply localized heating of living tissues and caused selective heating of bone cortex and marrow as does no other source of energy thus far used for medical diathermy. They demonstrated that ultrasonic application obliterated epiphysial lines and because of this destructive effect should not be used over growing bones.

In view of the frequency with which ultrasonic energy has been used in neurologic conditions it is significant that the Mayo Clinic group concluded that when maximal doses of such energy were applied over the lower vertebrae of dogs, there occurred destructive effects in the spinal cord resulting in paralysis of the hind legs and tail. Ultrasonic radiation of the sciatic nerve caused a striking decrease in action potentials but had no greater effect on conduction velocity of the nerve than that produced by other forms of heat. The destructive effect of ultrasonics on the spinal cord was much greater than that observed in peripheral nerves. Severe tissue damage was observed also on hair follicles and testes.

Buchtala[6] states that the application of ultrasonic waves to the heart or cervical ganglions may induce an abnormal cardiac rhythm and should be avoided in cardiac disease. Pregnancy is a contraindication to ultrasonic therapy. It is stated that hemorrhage into the eye and detachment of the retina have been caused by such therapy.

These possible disadvantages of ultrasonic therapy cannot be disregarded. However, as Bauer[7] points out, although there is no doubt that large doses of ultrasonic energy may cause serious damage, the danger is negligible so far as the ordinary practitioner is concerned because modern equipment has a well controlled energy output. The dosage used is well below the critical level and is practically self limited because pain which cannot be disregarded is felt and complained of by patients as soon as a dangerous dosage level is approached. Experience bears out the contention that ultrasonic therapy is a safe procedure if it is carried out within the limits of therapeutic dosage in properly selected cases. In one European clinic 6000 treatments were given with no untoward results. Friedland[8] carried out 1,477 ultrasonic treatments on 141 patients during a year without causing any damage.

Technic

If successful results are to be obtained from the use of ultrasonic energy a suitable technic must be observed. This subject has been dealt with in great detail by Bauer,[9] whose wide experience in this field of therapy lends weight to his observations. A number of factors require consideration if a technic is to be effective: (1) choice of frequency. This makes it possible to vary the number of waves per given volumes of tissue and to influence absorption; (2) the type of wave; (3) the intensity; (4) type of sound head; (5) method of application; (6) duration, and (7) number of treatments. The success of ultrasonic therapy depends on careful attention to the details of treatment.

The determination of proper dosage is of prime importance when ultrasonic therapy is used. A practical method of estimating the limits of dosage is the subjective sensation of pain experienced by the patient. Whenever

the output is too great or improperly directed, deep pain may be experienced at interfaces, as already described. If the coupling between the sound head and the skin is imperfect, surface burning and pain are felt. For effective treatment, more accurate procedures for determining dosage must be employed. This is necessary especially since it is generally conceded that the dosage indicators on most ultrasonic apparatus fail to furnish an accurate gauge of the amount of energy applied.

Ultrasonic dosage is measured in watts per square centimeter of the transducer face. The total amount of energy delivered by a sound head is determined by multiplying the watts per square centimeter decided on by the total area of the sound head in square centimeters. For example, if the area of a sound head measures 5 sq. cm. and it is decided to employ a dose of 1 watt per square centimeter, the total amount of energy delivered by the sound head is 5 watts. A therapeutic dose is regarded as small when it comes within the range of 0.5 to 1.5 watts/cm.^{2} Medium doses range from 1.5 to 3 and large doses from 3 to 6 watts/cm.^{2} Experimental and clinical observations indicate that although the larger doses when properly applied to some individuals may be used with safety, a dose of 1.5 watts/cm.^{2} is the upper limit of a safe dose by which even temporary destructive changes in tissue can be avoided. The total area of the surface to be treated must be taken into account, as well as the area of the sound head face, in estimating the amount of energy that is absorbed per square centimeter of tissue. In other words, if the total energy output of 10 watts is employed over an area of 20 sq. cm. the energy absorption per square centimeter of surface will be only 0.5 watt.

The ability of a tissue to dissipate the heat produced by ultrasonic energy determines the limit of its thermal tolerance. It is, therefore, useful to be able to apply ultrasonic energy either as a continuous wave or as intermittent pulsating waves. In the latter form of application an interval occurs after each emission of energy which allows the heat generated to be dissipated. Much of the ultrasonic equipment used does not provide for these two types of waves. This is not a serious defect, since there are many who are not impressed with the advantages of pulsating emissions.

Two principal treatment technics are employed: (1) the stationary and (2) the stroking or massage method. Both methods have their advantages and limitations. With the stationary method the greatest effect can be obtained locally from small amounts of ultrasonic energy. It is particularly useful when it is desirable to apply ultrasonic therapy to nerve roots and sympathetic ganglions. It is recommended especially by the advocates of the neurotrophic theory of ultrasonic action. As the static method brings about the greatest interference effects, the limit of tolerance to such treatment depends on the distance of interfaces such as the periosteum from the surface being treated. If the intensity and duration of a stationary treatment are too great, pain is experienced. If this occurs, the intensity must be reduced because it is important to avoid the production of pain at interfaces.

The massage method is the one most generally employed. It reduces or eliminates interference effects and brings about a less intense type of heating in a larger area. The reaction to treatment by any method varies with the amount of energy used, the size and character of the area under treatment and the individual variations of the patient.

When submersion treatment is employed, the part to be treated is immersed in water, along with the watertight sound head. The transducer kept at an appropriate distance from the part may be held stationary, or be slowly moved back and forth on a line parallel to the surface being treated. The submersion technic is useful when direct contact of the rigid sound head with the part to be treated is inadvisable or when the surface to be treated is so uneven that adequate coupling with a rigid metal sound head cannot be obtained except through the use of water. The difficulties presented by uneven surfaces can also be overcome by fitting the sound head with an elastic diaphragm or a bag of thin rubber filled with boiled water. An air-excluding coupling medium must be used in order to insure satisfac-

tory contact with the surface to be treated. The best results from ultrasonic therapy, as might be expected, are obtained by those who employ accurate dosage and pay careful attention to all the details of technic.

Therapeutic Value

At the International Congress on Ultrasonics held in Germany in 1949, 48 disease conditions were discussed as appropriate for ultrasonic therapy. This indicates the extent to which this form of treatment has been employed by certain clinicians. During the past five years a large number of clinical reports, from European and English clinics, claim excellent results from ultrasonic therapy in a large and diverse group of diseases. Fifty per cent of the patients who received ultrasonic therapy were reported as either markedly improved or completely cured. The majority of these reports are unconvincing, since they lack evidence of any truly critical or scientific evaluation of ultrasonic therapy. For the most part the observations have been uncontrolled and the conclusions have been based largely on clinical impressions.

The medical profession of this country has been much more conservative and slower to wholeheartedly embrace ultrasonic therapy. It would seem that the experimental work carried on in our institutions and clinics, which has indicated the contraindications and possible dangers of ultrasonic therapy, has exerted a deterrent effect on the widespread clinical use of this type of energy. Nevertheless, as more and more physicians in this country have become interested in this treatment, there has developed a growing belief that ultrasonics possess definite therapeutic possibilities.

It is admittedly difficult to evaluate the results of ultrasonic therapy. This is so because the conditions which lend themselves best to such treatment are, for the most part, of uncertain etiology, run long and variable courses subject to spontaneous exacerbations and remissions, are self limited, and often are favorably influenced by a variety of treatments. Furthermore, many patients while receiving ultrasonic therapy are concurrently under other forms of treatment. In order to establish the value of ultrasound as a therapeutic tool, more controlled clinical observations are needed. This can be accomplished by comparing the results of ultrasonic therapy in any given condition with those obtained with older and better recognized forms of physical treatment.

In this country such a controlled study has been carried on by Friedland and associates[8] on 141 patients suffering from conditions generally regarded as suitable for ultrasonic therapy. Control groups were given the orthodox forms of treatment and the results compared. Friedland and his group conclude that ultrasonic radiation has an analgesic effect which is no greater than that produced by other physical agents. They observed no detrimental effects in 1,477 applications. They regard ultrasonic therapy as local treatment which cannot influence the underlying cause of disease and is without specific virtue.

Therapeutic Indications

A variety of conditions have been subjected to ultrasonic therapy. Chief indications for its use are the arthritides and allied rheumatoid conditions, including myositis and fibrositis, and disorders of peripheral nerves such as neuritis, especially that involving the sciatic nerve, neuralgia, causalgia, coccygodynia and pain in phantom limbs.

Arthritides

The results obtained with ultrasonic therapy in arthritic conditions involving peripheral joints are indicated by the reports of Barth and Wachsman,[10] Demmel,[11] Ungeheuer[12] and other European observers who collected the records of 456 cases in which 38.4 per cent of the patients were reported as cured or markedly improved and 39.1 per cent improved; the balance were unimproved or worse, or presented uncertainty in diagnosis. On the other hand, Friedland[8] in a small number of cases of peripheral rheumatoid arthritis treated by ultrasonic therapy reports that the pain-relieving effect of this type of treatment was not different from that obtained with other conventional physical agents. He failed to observe the relief of any symptom other than pain.

Our limited experience in the treatment of rheumatoid arthritis corresponds to that of Friedland. Buchtala,[4,6] reporting on 287 cases of painful disease of joints, concluded that relief from pain and restoration of function were obtained more rapidly by ultrasonic therapy than by x-ray therapy. He admits that, as a rule, rheumatoid arthritis does not react satisfactorily to ultrasonic energy, and that relief of pain is apparent only after 20 or 30 treatments and even then relapse is common.

The largest number of cases of Marie-Strümpell disease treated with ultrasonic energy was reported by Hintzelmann.[13] In a series of 800 he records improvement in 77.5 per cent, indicated by increase in mobility of the spine and improvement in chest expansion. Of the remaining cases he records only 4 per cent cured, 18.3 per cent unchanged and 0.2 per cent made worse. Evidence of improvement most often observed was the subjective relief of pain. Hintzelmann's observations were not confirmed by Friedland,[8] who found ultrasound to be of no greater benefit than other physical agents. In Marie-Strümpell disease Hintzelmann employed massage treatment along the spine using an energy output of 20 to 30 watts per 10 cm.^{2}

An extensive series of patients suffering from osteoarthritis has been subjected to courses of ultrasonic therapy. In a series of 924 cases, 41 per cent were improved and the remainder unchanged. Since 1950 it appears that most European clinicians in the treatment of osteoarthritis have supplemented local treatment applied to the affected joint by the stationary application of ultrasound to the spinal nerve roots. It is recommended that for shoulder joints the nerve roots of C_4 to T_2 should be treated; for the elbow, roots of C_4 to C_6; for the wrist and finger joint C_5 to T_2, for the hip L_3 to L_5, for the knee T_{12} to L_3, and for the ankle S_1 to S_4. It is stated that such treatment brings about better results than local treatment alone. In the small series of patients suffering from degenerative joint disease that has been under personal observation, we have found, along with Friedland and others, no greater improvement with ultrasonic therapy than with other types of physical therapy usually employed. It must be admitted, however, that as yet we have not employed sound treatment of nerve roots in our patients suffering from degenerative joint disease.

Myositis

Lumbago and other forms of myositis and fibrositis are well adapted to sound treatment. In the collected reports cited by Bauer[7,9] of 300 cases of lumbago and fibrositis, 51 per cent were cured, 34 per cent improved and 15 per cent unchanged. The quick relief of pain, even in chronic cases, and early restoration of movement are emphasized. It must not be overlooked that in these conditions spontaneous recovery is not unusual. In the few patients with myositis to whom we have administered ultrasonic therapy, relief of pain has not been obtained any more rapidly than in patients who received radiant heat in some form and massage.

Bursitis

There is considerable evidence that subdeltoid bursitis, especially in the acute stage, is treated satisfactorily by ultrasonic therapy. Personal communications from physicians who have employed this type of therapy extensively in bursitis are enthusiastic over the prompt relief of pain obtained, especially in acute subdeltoid bursitis. In evaluating any form of treatment for bursitis it should be borne in mind that many acute cases undergo spontaneous recovery. Other forms of therapy including x-ray irradiation, short wave diathermy and negative galvanism have been credited with results as dramatic and prompt as those attributed to ultrasonic therapy. Our observations lead us to believe that sound therapy is often effective in the acute stage of subdeltoid bursitis as a means of relieving pain and consequently allowing a return of shoulder motion. However, many cases have proved as resistant to this type of treatment as they have to other physical measures. The analgesic effect, already noted, of ultrasonic therapy is probably responsible for early relief of pain. In the treatment of bursitis it has been our practice to employ massage

technic with an energy output of 0.5 to 1 watt/cm.^{2} The treatment is given daily, sessions lasting from 5 to 18 minutes.

Diseases of Peripheral Nerves

In disturbances involving peripheral nerves, ultrasonic therapy is regarded by many as of particular importance. It has been extensively used in the management of sciatica and neuritis of the components of the brachial plexus.

The success of ultrasonic applications in peripheral nerve disorders depends on the cause of the neuritis. It is our experience that when neuritis—sciatica, for example—is due to spinal nerve root compression from a herniated disk, osteoarthritic changes or some other structural lesion the results of the treatment are discouraging. The same applies to lesions involving the cervical nerve roots and the brachial plexus. Neuritis from other causes is more likely to respond satisfactorily. Disorders of trigeminal and occipital nerves are said to react unfavorably to ultrasonic therapy. In treating neuritis of the brachial plexus and sciatica the technic that is regarded as most satisfactory is the stationary method with the sound waves so directed that they reach the spinal roots of the involved nerves and/or the adjacent sympathetic ganglions. For such treatment the dosage should be small, 0.1 to 0.25 watts/cm.^{2} When the massage technic is employed along the course of the nerves a larger dose (2 to 4 watts/cm.^{2}) should be used.

It has been shown that therapeutic doses of ultrasonic energy can induce vasodilatation and hyperemia. These changes are not wholly due to local heat production, but are in part the result of the neurotrophic action of ultrasonics which some investigators believe has been satisfactorily demonstrated. This vasodilating effect is the basis for the use of ultrasonic therapy in peripheral vascular disease by Tschannen[14] and others. Vascular disorders in which spasm is the dominant factor respond to ultrasonic radiation much better than those in which vascular elasticity has been lost. Some cases of thromboangiitis obliterans and Raynaud's disease have shown favorable response, whereas vascular sclerosis has been unaffected. Tschannen has observed the skin temperature of a lower extremity to increase 0.5 to 1° C. under ultrasonic treatment. He reports the most rapid and satisfactory improvement in vascular disease of the leg from small doses of ultrasonic radiation to the spinal nerve roots at L_5 to S_5.

Neural Effects

The remote indirect effects of ultrasonic waves produced via the nervous system have been taken advantage of in the treatment of a variety of conditions which include pulmonary tuberculosis, bronchial asthma, essential hypertension and peptic ulcer. This aspect of ultrasonic therapy has been well reviewed by Stuhlfauth,[15] who has carried on suggestive fundamental investigations on the neural effects of ultrasonic waves.

Pyogenic Infections

It is reported that inflammatory conditions and pyogenic infections of soft parts, particularly the skin and its appendages, have been favorably influenced by ultrasonic therapy. Furuncles, carbuncles, paronychia, sinuses and abscesses, including mastitis and breast abscess, have been so treated. The most significant result is the prompt relief of pain accompanied by more rapid demarcation and decrease in inflammatory swelling. Continuous emissions are preferable to massage technic, with small dosage (0.1 to 1 watts/cm.^{2}) applied for two to four minutes twice daily. It is worthy of note that several authors suggest that it is advisable to combine adequate antibiotic therapy with ultrasonics.

Malignant Growths

Efforts to favorably influence malignant growths by ultrasonic radiation have been unsuccessful. Experimental observations on transmissible tumors of animals have shown that ultrasonic energy does not inhibit such growths. Small doses of ultrasonic therapy actually stimulated intracutaneous adenocarcinoma of mice. The recent studies of Schroeder, Herrick and Karlson[16] on the effect of ultrasound on the transmissible Walker rat carcinoma furnish additional evidence that

there is no selective destructive effect of ultrasonic waves on malignant cells. With excessive doses, these observers were able to demonstrate destruction of the skin and a portion of the tumor with, however, a continued growth and expansion of the neoplasm to adjacent tissue. The treatment of malignant tumors by ultrasonic radiation is definitely contraindicated. Furthermore, by employing ultrasonic therapy the use of effective, recognized forms of treatment such as surgery and irradiation with x-rays or radium may be delayed dangerously.

Clinical Experience

In a small series of patients treated in the Department of Physical Medicine and Rehabilitation of the Hospital of the University of Pennsylvania during the past six months, the following conditions were subjected to ultrasonic radiation: spondylitis deformans, rheumatoid arthritis, hypertrophic osteoarthritis, subdeltoid bursitis, sciatica, postherpetic neuritis, hysterical neuralgia, amputee stump pain, myositis, fibromyositis, causalgia, condensing osteitis of the ilium, and frozen shoulder following cerebral vascular accidents.

In every patient the treatment consisted of the massage technic with a rigid transducer head. The doses given ranged from 0.5 to 1.0 watts/cm.^{2} for periods of from five to eight minutes.

The only dramatically good results were obtained in several cases of acute subdeltoid bursitis. In general it has been our experience that during this period under consideration as many patients showed significant improvement after changing from ultrasonic therapy to other forms of heat as improved when the reverse procedure was followed.

Summary

1. Ultrasonic radiation has undoubted therapeutic possibilities.

2. The results obtained from ultrasonic treatment are due largely to the thermal effects of this agent. Ultrasound definitely produces certain nonthermal effects. These are still poorly understood. There is no conclusive evidence that they bring about therapeutic results. The heat produced by sound waves is more penetrating and can be beamed with greater accuracy than other types of heat.

3. Ultrasonic energy when applied to living tissue in sufficient dosage can produce irreversible destructive changes.

4. Because of these potential risks there are definite contraindications to using ultrasonics.

5. The different technics developed for the therapeutic application of sound waves should be understood and followed. Careful consideration must be given to dosage. Ultrasonic treatment should be administered only by experienced personnel.

6. Ultrasonic therapy has been used in a wide range of diseases. It finds its greatest value in the treatment of the arthritides and various rheumatic conditions, disorders of peripheral nerves and possibly vasospastic peripheral vascular diseases and pyogenic infections of soft parts.

7. The cures and marked improvement in many other conditions reported by enthusiastic advocates of sound therapy have not been confirmed by the majority of other observers.

8. Available evidence indicates that ultrasonic radiation is a local therapy without specific biologic properties, capable of producing analgesic effects without influencing the underlying causes.

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The Microbiologic Agents of Infectious Disease

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Infectious diseases are considered in terms of interactions between the human host and the microbiologic agents with which the host is living in symbiotic or parasitic relationship. Bacteria are seen to be cells in essentials as other cells. Possible interventions of the physician on behalf of the human host are defined.

STUART MUDD

THE invitation to prepare this article has been accepted only with grave misgivings, for one realizes that those who may read it are dealing with the clinical manifestations of infectious disease in a very practical way, whereas this discussion will be concerned with the biologic foundations from which the manifestations arise. However, understanding of the structure, physiology and reproduction of bacteria and viruses is in a state of such rapid development that the conceptions current when even the youngest medical practitioners were students are now undergoing drastic alteration. These evolving insights are not without relevance in practical therapeutics.

Infectious diseases are now recognized as special cases of parasitism, of the biologic association of human hosts with microscopic organisms, to the detriment of the hosts. Survival is of course the biologic objective of both host and parasites. The host species is commonly regarded as at the top of the evolutionary scale, and the bacterial or viral parasites as at the bottom of that scale. The role of the physician is that of a partisan in this biologic struggle; it may reasonably be assumed that the effectiveness of his intervention in behalf of the host will in general be increased by his understanding the natures of the organisms and the mechanisms of the struggle in which they are engaged.

Parasitism and Disease

The concept of infectious disease as parasitism was first clearly formulated by Theobald Smith[1] and has recently been restated with admirable conciseness by Francis.[2] Successful parasitism and hence the continuity of the chain of infection imposes four biologic necessities on the parasite species.

1. The parasite must gain entrance to the host. The well known portals of entry are: for the opportunist invaders such as pyogenic cocci, defects in skin or mucous membranes, traumatic or surgical wounds; for droplet or dust-borne pathogens, such as pneumococci, streptococci and tubercle bacilli or the air-

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borne viruses of influenza, measles or chickenpox, the respiratory tract; for water-borne and food-borne pathogens, such as the typhoid, paratyphoid, dysentery and cholera organisms, the digestive tract; for the agents of venereal disease, the genitourinary tract; for the parasites disseminated by arthropod vectors, such as the plague bacillus, the rickettsiae, or the viruses of the encephalitides and yellow fever, the integument penetrated by biting.

2. The parasite must reach a suitable site in or on its host and there multiply. If the parasite can establish itself without overt disturbance of the host it may become a part of the benign normal flora, or alternatively may make of the host a resistant carrier of agents which may cause disease in others. The physician himself may become such a healthy carrier and hence an unconscious vector of infections. More often the establishment of the parasite causes the manifest disturbances which constitute infectious disease and which are a principal focus for clinical medicine.

3. The parasite must find a suitable means of exit from its host. For the opportunists this may be the discharge from wounds or superficial lesions, infected dressings or bedclothes and the like; for respiratory pathogens, the respiratory tract secretions discharged in sneezing, coughing or merely talking, or through contact with objects taken into the mouth; for the intestinal pathogens, largely the feces; for the venereal agents, lesions mostly in the genitourinary tract; for the vector-borne diseases, bite of the specific arthropod vectors.

4. The parasites must find effective means of transmission to new hosts. In interrupting these chains of transmission the physician as practitioner or as public health officer has many and strategic opportunities for intervention. He can see that superficial wounds are cleansed and that deep wounds are debrided, and that dust from infected bedclothes and dressings does not disseminate infection. In addition, education, ultraviolet barriers, isolation, proper masks and other means can reduce air and droplet contamination; sewage pollution can be prevented, and venereal prophylaxis can be practiced. Sanitary control of insect vectors in Cuba during the Spanish-American War and in the Canal Zone, the elimination of urban yellow fever in South America and the control of rickettsial diseases during and following World War II have constituted some of the most dramatic triumphs of preventive medicine.

In general the evolution of the parasitic relationship tends toward mutual tolerance of host and parasite[1] and hence toward greater chronicity of disease, as exemplified by the trend over the centuries toward mildness and chronicity in tuberculosis and syphilis. Diseases which are too rapidly fatal tend not to fulfill the biologic requirements of the parasite and hence to die out, as for example pandemic influenza, whose causal agent may well have overdone its parasitism and have become extinct.

Bacteria, Rickettsiae and Viruses as Cells

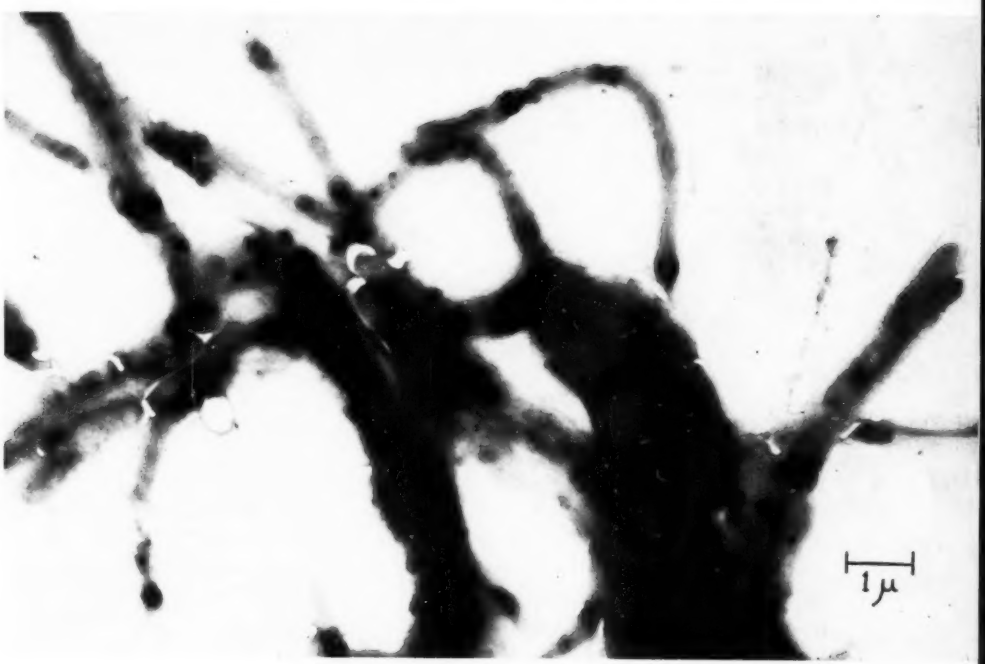
The complex nature of the human organism and its reactions to the stresses of infection will be referred to in only a few relevant details. The new insights which constitute the dramatic developments of the past decade in microbiology concern recognition of bacteria, rickettsiae and at least some viruses as cells and as organisms. New tools, notably the electron microscope and the phase contrast microscope, and improved cytochemical procedures, have made it possible to visualize the structure and internal organization of the microparasites.

Cellular organization of bacteria—Throughout the range of pathogenic bacteria we find that bacteria are cells in the full sense familiar in higher organisms.[3,4] Bacteria have cell walls which provide mechanical protection to the protoplast within. These range from the rigid wall of *Bacillus anthracis* to the delicate, ductile, lipoid-rich wall of *Mycobacterium tuberculosis* (Figures 1 and 2) and the delicate periplast of *Treponema pallidum*. Measurement in electron pictures of *Myco. tuberculosis avium* has given a wall thickness of 0.023 micron.[5]

The protoplast of the bacterial cell possesses a definite limiting membrane which can

FIGURES 1 and 2. Electron picture of *Mycobacterium tuberculosis hominis*, strain H37Rv. X 10,000. RCA Plate #6372. Microcolony grown four days on collodion overlying 5 per cent glycerol agar. Fixed one minute over vapors of 2 per cent OsO_4. Held in desiccator for 12 hours.

Figures 1 and 2 are darker and lighter prints from the same plate. In Figure 1 the osmiophilic surface films surrounding the bacillary cell walls are visualized. In Figure 2 the internal mitochondrial granules are seen. Preparation by Loren C. Winterscheid.



The electron micrographs in Figures 1 through 5 were taken by Dr. James Hillier of the RCA Research Laboratories, Princeton, New Jersey.

be demonstrated as a distinct structure and differentially stained. From measurements of electron micrographs Knaysi[6] gives the thickness of the cytoplasmic membrane as 0.02 micron. The cytoplasmic membrane has been discussed by Mitchell[7] as an osmotic barrier regulating active and passive transfer of materials into and from the bacterial cell:

"To summarize, the evidence suggests that Claude Bernard's concept that all free living organisms must possess a relatively isolated internal environment is true for the bacteria. As well as offering passive resistance to the movement of substances into and out of the cell, the osmotic barrier is the seat of processes of active transfer which maintain the differences of composition of the internal and external environments in actively metabolizing or in growing cells; and the steady concentrations of the substances within the cell generally represent steady-state conditions and not equilibria."

The protoplast and its cytoplasmic membrane are all that one sees in routinely stained preparations of bacteria. The cell wall and other peripheral structures, as capsules and flagella, may be stained by special technics, but are not visualized in routine gentian violet, methylene blue, Gram or acid-fast stains.

Examination of living coliform rods with the phase contrast microscope[8] reveals a characteristic pattern of alternate dark and light zones. The dark zones are at the poles and in the centers of the cells; the light zones are intermediate in position. The same pattern may be revealed by electron micrographs (Figure 3). Examination of available evidence leads me to make the categorical statement that the light intermediate zones are the sites of the bacterial nuclei, and the dark polar and central areas are the sites of mitochondria, organelles in which processes of aerobic respiration, and doubtless associated synthetic processes, are organized.[4,9]

Refractile, spheroidal to ellipsoidal granules were admirably described by Robert Koch in 1884 in his original description of *Myco. tuberculosis* and interpreted as spores. They have since been described by innumerable investigators using dark field, fluorescence and phase microscopy and electron microscopy and variously interpreted. The evidence which leads me to interpret these granules as mitochondria is presented in references 4 and 10.

Reference to current works on bacteriology and bacterial cytology will show clearly that the physiologic and genetic behavior of bacteria has so much in common with the cells of higher organisms that assumption of a similar mechanism of genetic continuity and genetic change becomes almost a logical necessity.[11] Yet all but the most up-to-date works state that evidence of mitotic nuclear division in bacteria is still lacking.* Within the past two years the evidence that bacteria do, indeed, possess mitotic nuclear division has been forthcoming particularly in the cytologic studies of E. D. DeLamater and his associates.[4,13-17] (Figure 6.)

DeLamater, studying representatives of a number of bacterial families with the aid of refined cytologic technics, has demonstrated the classic sequence of mitotic nuclear division, occurring in miniature. The chromosomes may even be counted and their longitudinal splitting preparatory to alignment on the metaphase plate observed and photographed.[4] It appears that in the species thus far studied the vegetative nuclei are in the haploid state, although evidence suggesting nuclear fusion to form diploid zygotes has been observed under certain experimental conditions.[16] As had earlier occurred in classic genetics, analysis of genetic behavior in bacteria began before there were any adequate cytologic observations as a structural basis for that behavior. DeLamater's studies constitute an important beginning at closing this gap in our knowledge of bacteria.

In the cases of rickettsiae and viruses an even wider gap exists, however. Electron microscopy[3,18,19] has demonstrated beyond question that rickettsiae, the known animal viruses and bacterial viruses possess an elementary structural differentiation into external limiting wall and inner material. In the cases of rickettsiae and the larger animal viruses, such as those of the lymphogranu-

*The tenth edition of Zinsser's "Textbook of Bacteriology"[12] furnishes a gratifying exception.

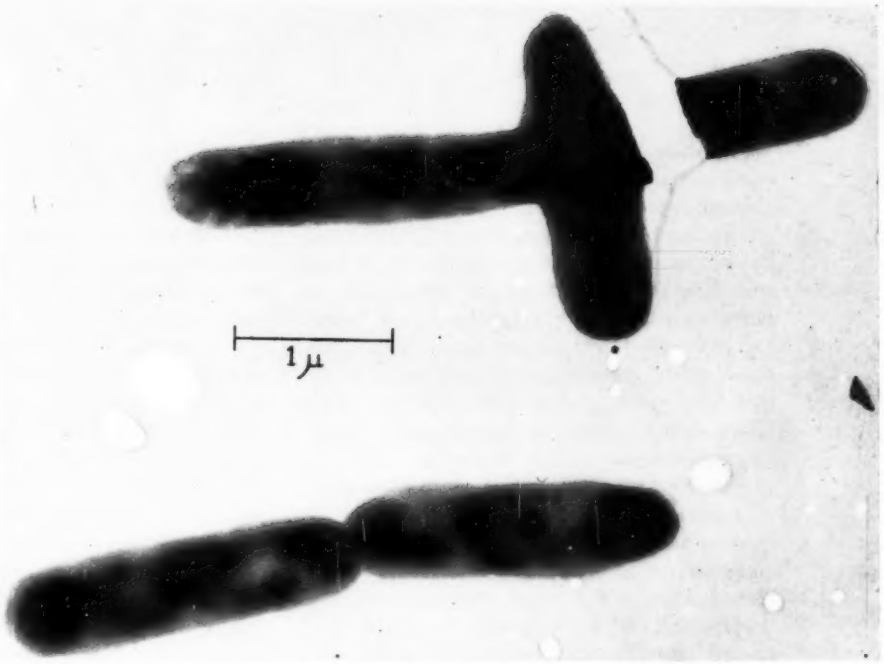


FIGURE 3. Cells of uninfected *Escherichia coli* strain B. X 30,000. RCA Plate #5868. Grown 90 minutes on collodion overlying tryptone yeast extract agar. Fixed one minute in vapors over 2 per cent OsO_4. Dialyzed one hour over distilled water. Stored in desiccator over $CaCl_2$. The dark spheroidal areas at the poles and in the centers of the cells are the sites of the mitochondria; the light intermediate areas are the sites of nuclei. The collodion mount in the upper part of the picture has split, breaking open a colon bacillus. Attention is directed to the jagged line of fracture of the cell wall. (Preparations in Figures 3 to 5 by E. H. Beutner and P. E. Hartman.)

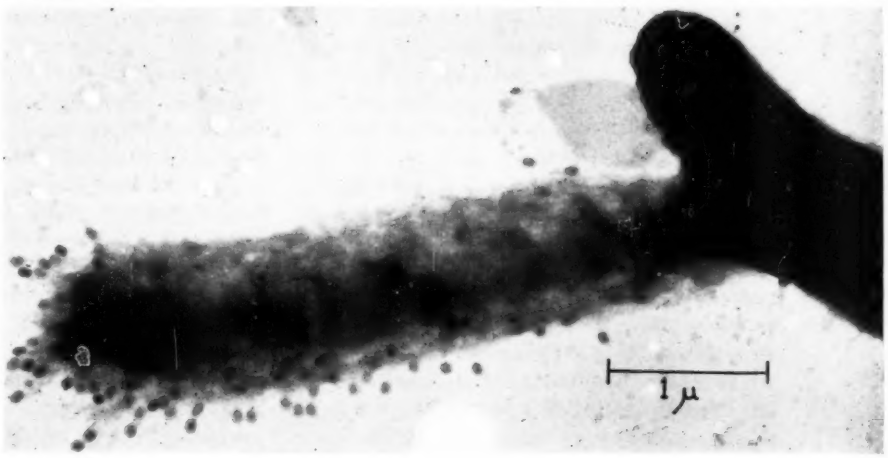


FIGURE 4. Cells of *Esch. coli* B, 15 minutes after infection with T2r coliphage. X 30,000. RCA Plate #5858. The phage particles are adsorbed by the tips of their "tails." The internal organization of the infected cell is profoundly altered from the normal.

loma-pneumonitis-trachoma group and the pox viruses, it is entirely possible that further structural differentiation into equivalents of nucleus and mitochondria may be discovered, if only technical means can be refined adequately for the task. In the case of the best studied bacterial viruses (bacteriophages), however, we clearly have organization in even simpler terms, since the chemical contents of these elementary infectious particles can be accounted for quantitatively in terms of protein and desoxyribose nucleic acid, the latter, either alone or as nucleoprotein, bearing the hereditary determiners.[20] Finally, the plant viruses, such as that of tobacco mosaic, are macromolecular crystals of a single chemical substance, pentose nucleoprotein.[19]

The Microparasites as Organisms

Adaptations and counteradaptations to parasitism—In pathogenic forms it is the periphery of the cell which comes into immediate contact with the cells and fluids of the host organism. The immunochemical composition and arrangement of peripheral components of the bacterial cell thus become significant in

host-parasite interactions and indeed may become critical in the struggle for survival between host and parasites.[4]

The peripheral components of pathogenic bacteria are in general antigens; that is, they stimulate the production in their hosts of globulins which have the property of chemical complementariness to themselves. As a result of this complementariness the immune globulins enter into specific chemical combination with their antigenic counterparts. These combinations are in general protective to the hosts and inimical to the pathogenic bacterial cells; these cells may be aggregated, may suffer direct chemical injury such as antibody-complement bactericidal action, and almost invariably become endowed with surfaces which may be wetted by the protoplasm of and hence be phagocytized by the sentinel, phagocytic cells of the host.

A necessary (although of course not a sufficient) condition for survival of bacteria within the tissues and fluids of their hosts is that they shall not be prematurely destroyed by phagocytes. The possession of surfaces which are not wetted by the protoplasm of phagocytic cells or which are otherwise inimical to the action of phagocytes has survival value for invasive bacteria.

Actually invasive pathogens do have such surfaces, and these have been acquired through a striking variety of chemical surface components, which may be in the form of special antigens in the cell wall, or of extracellular capsules or mucoid material. The typhoid bacillus in virulent strains has a special antigen, in particular along the sides of the cell wall, which prevents interaction between the ordinary somatic antigens and their antibodies. The somatic antigens of the salmonellae are complex carbohydrate-protein-phospholipid molecules owing their immunochemical specificity in particular to the carbohydrate component.

Invasive strains of *Escherichia coli* have a variety of special peripheral components classified by Kauffmann[21] in the category of K (capsule and envelope) antigens. Ordinary symbiotic or laboratory strains of *Esch. coli* are usually without K antigens. The capsular antigens of Friedländer bacilli and some other encapsulated coliforms have been characterized as polysaccharides.

Streptococcus pyogenes, in strains pathogenic for man, possesses an antigen at the surface of the cell wall which is a protein of quite special character. Pathogenic strains of *Str. pyogenes* have evolved an even more effective protective device in the form of an extracellular mucoid envelope of hyaluronic acid. Since hyaluronic acid is a normal component of mammalian connective tissues, the bacterial hyaluronic acid is not a foreign substance and antibodies do not form against it.

Virulent pneumococci are enclosed in an extracellular gel which is composed of thread-like molecules of polymerized carbohydrates chemically specific for each pneumococcal type. These capsules are not spontaneously wetted by the protoplasm of phagocytes unless permeated by the homologous type of specific immune serum. *B. anthracis* possesses an extracellular capsule which consists of a polypeptide made up of the "unnatural" amino acid d(−) glutamic acid.

The cell wall of the virulent human and bovine varieties of *Myco. tuberculosis* is enveloped in a delicate superficial film. This film causes adjacent cells of a developing culture to cohere and endows the culture with a distinctive growth habit in the form of serpentine cords.[22] (See Figure 1.) The substance constituting this film is lipoidal in nature and is endowed with a subtle primary toxicity for the phagocytes of animals susceptible to tuberculosis.[23]

The periphery of invasive pathogenic bacteria, then, may be composed of protein, carbohydrate or lipid of special characteristics but possessing in common the significant attribute of being inimical to the actions of phagocytes. To imagine how to deal with parasitic cells presenting so diverse an array of surfaces would certainly tax the ingenuity of a physical chemist. As a matter of fact, however, solutions of great elegance have been evolved in nature.

The most generally effective solution has been to make the diverse alien surfaces of the invasive pathogens all alike and readily

wettable by phagocytic protoplasm. This is accomplished by the host's elaboration of immune globulins (antibodies), each with specific chemical affinity for the corresponding bacterial antigen. The new surfaces formed by the interaction of bacterial surface antigens and homologous antibodies are, in the words of G. B. Shaw, highly "palatable to leucocytes." The globulins of normal human serum possess to some extent this protective attribute of adsorbing to the surface of foreign particles. The efficiency of combination with bacterial surface components is greatly increased by the specific chemical affinities of antibodies elaborated in response to the stimulation of bacterial antigens.[24]

Bacteria with potentialities for successful invasion must, however, gain access to tissues or body fluids under many circumstances in which adsorbed normal globulins are inadequate to promote phagocytosis and in which there has been insufficient time for the elaboration of the more efficient immune globulins. A phenomenon has recently been described in detail by W. Barry Wood which deserves to be classed with antibody formation as a protective device of elegance and great survival value. This is called by Wood "surface phagocytosis." Phagocytic cells have long been known to possess the power of creeping along the fibers of fibrin clots and over the surfaces of endothelial cells of blood vessels, particularly when inflamed. The protoplasm of phagocytic cells readily adheres to or spreads along the cells and fibers of the usual environment of such cells. If phagocytic cells collide with freely suspended pneumococci or Friedländer's bacilli in the absence of immune serum, phagocytosis does not occur. However, the beautiful experiments of Wood and associates[25] have shown that if a phagocyte, creeping along a surface in a lung alveolus, lymph node or blood vessel, encounters the same bacterial cells in contact with the surface over which the phagocyte is spreading, the bacteria are enveloped in the protoplasm of the phagocyte. Surface phagocytosis must preserve man and other host species from countless infections.

In addition to the peripheral components which protect pathogenic bacteria from action of the host's defenses, these microparasites may elaborate various exotoxins, endotoxins and physiologically active metabolites which specifically disturb the body's normal physiology. Familiar examples are the exotoxins of the organisms of diphtheria, tetanus, botulism and gas gangrene, the endotoxins of the typhoid-paratyphoid-dysentery group, the erythrogenic toxin, hemolysins and leukocidin of *Str. pyogenes,* and the coagulase of pyogenic staphylococci.

Viruses also may elaborate highly toxic components; an example is the neurotoxic action of the virus of influenza, even though the lesions of that disease are in the respiratory tract. Viruses also possess surface components for attachment to the specific receptor sites of the cells they parasitize, and apparently lytic enzymes which aid in penetration into the host cells. The most remarkable example thus far worked out is that of many coliphages, which possess ultramicroscopic stems by which they attach themselves to specific receptor sites on the colon bacillus host (Figure 4). The gene-bearing desoxyribonucleic acid contents of the phage head are then actively injected into the colon bacillus,[26] and there divert the metabolism of the host cell to elaboration of several scores or hundreds of phage particles (Figure 5). These particles are liberated by lysis of the host cell and continue the chain reaction of infection, replication and lysis as long as susceptible host cells and the necessary environmental conditions may be available.

The Physician's Intervention

How then may the physician intervene in this Wellsian struggle of the microscopic and the ultramicroscopic, and what are the mechanisms through which his intervention may aid the beleaguered human host?

1. In general, use of all possible means for interrupting the chains of transmission. An instance which might well receive attention is the exchange of flora which may occur through the air of the busy physician's reception room.

2. Active immunization. Vaccination with

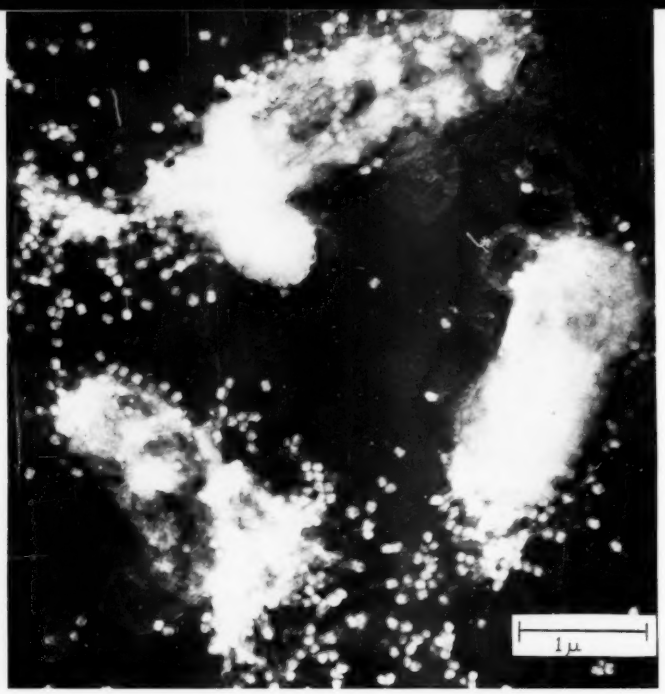


FIGURE 5. Cells of *Esch. coli* B, 25 minutes after infection with T2r coliphage. X 36,500. RCA Plate #5986. Three cells infected with T2r in process of disintegration. In each large numbers of intracellular phage particles are discernible and from each numerous phage particles appear to be escaping. From the cell toward the bottom four rounded processes have been extruded, one still filled with cytoplasm, the others empty cell wall. Filiform processes are everywhere. The external phage particles may be seen to comprise dense material within an external surface membrane which is continuous with the tail.

Figures 3 to 5 are from a systematic study of the sequences of change following infection of *Esch. coli* with T2 bacteriophage.[31]

Hemophilus pertussis stimulates production of antibodies which combine specifically with the antigens at the surface of the bacterial cells and aid in their destruction through antibody-complement action or through phagocytosis. Inoculation with tetanus or with diphtheria toxoid or, under circumstances of special risk, with scarlatinal toxin, elicits antibodies which specifically neutralize corresponding toxins. Vaccination with BCG stimulates the complex adjustments which increase resistance to tuberculosis. Vaccination with vaccinia, influenza or mumps virus elicits antibodies which may combine with the specific virus particles before they enter the host cells. The antibody-coated virus particles are susceptible to phagocytosis and their surface sites are probably blocked from attachment to the specific host receptor sites. Once actively immunized, the subject is able to give a specific immune response more quickly and more efficiently when challenged again (anamnestic response), particularly if resistance is recalled at suitable intervals by booster injections or by natural exposure.

3. Passive immunization. When the circumstances do not permit the more efficient protection afforded by active immunization, passive immunization may at times prevent the disease or reduce mortality, e.g., diphtheria antitoxin; gamma globulin against measles, epidemic hepatitis and poliomyelitis.[27,28]

4. The physician may on occasion utilize physiologically active metabolites of bacteria in therapy, e.g., streptokinase and streptodornase.

5. Therapeutics have of course been revolutionized by utilizing antibiotics, which are metabolic products of micro-organisms.

Susceptibility and Resistance to Antibiotic Therapy

"Comparative biochemical studies have shown that nutritional requirements, intermediary metabolism and synthetic processes are remarkably similar in all living cells, and the bacteria prove no exception to this rule."[29] Moreover, "all the knowledge gained during the past 10 years or so has converged toward the conclusion that the mechanisms of heredity are in essence the same in bacteria as in any other living organisms or, rather, cells."[29]

Successful chemical intervention in the host-parasite relationship requires that metabolic processes indispensable to the parasite be inhibited without interfering in equal measure with metabolic processes essential to the host. The basic similarities referred to doubtless in part explain why chemotherapy was so much later in emerging than were

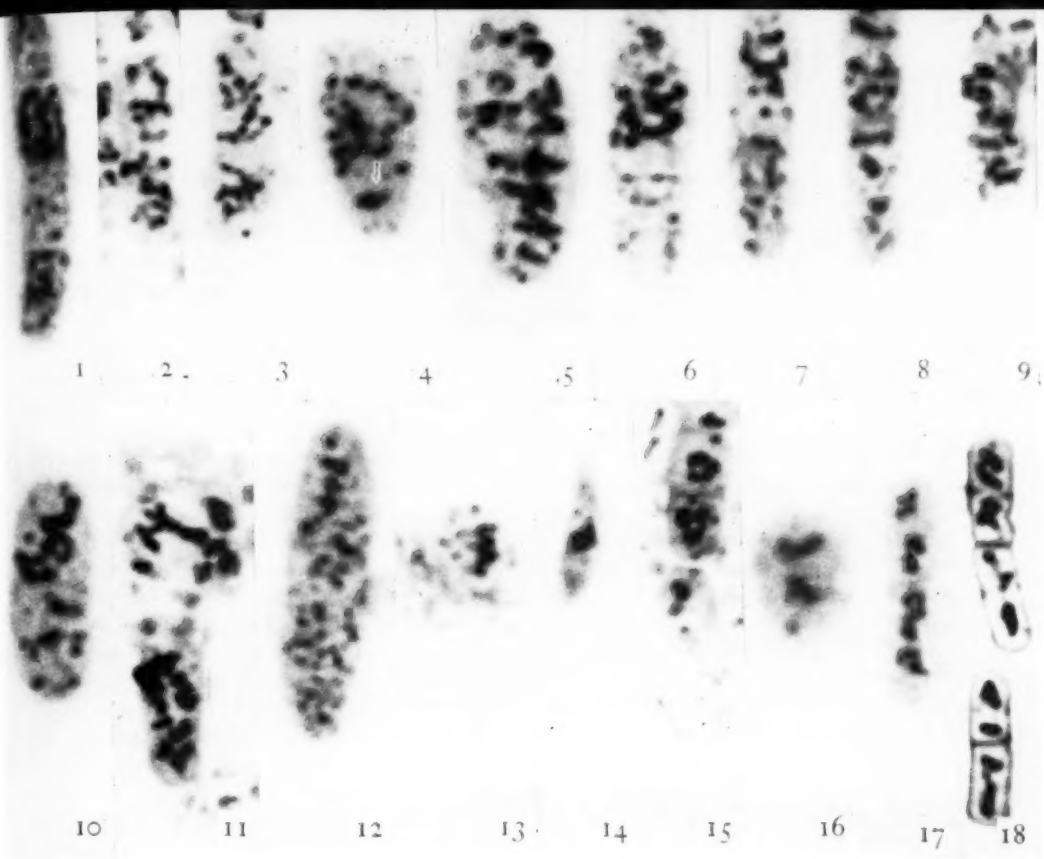


FIGURE 6. *Bacillus megaterium.* (x 6000.)

1. Multinucleate cell, partially crushed, with nuclei in both interphase and early prophase, in which the chromosomes can be seen (1) as delicate, tangled, beaded threads and (2) as denser, contracting, beaded threads.
2. Crushed cell showing chromosomes as contracting, beaded threads.
3. Chromosomes contracted to stiff, beaded bars. The beaded areas are thought to correspond to the chromomere areas of larger chromosomes.
4. Cell well crushed shows the chromosomes in middle prophase as tangled threads. The upper chromosome shows a satellite at its tip and the suggestion of a primary spiral.
5. A well crushed multinucleate cell. The second nucleus from the top shows three chromosomes, the central member of which lies transverse to the axis of the cell, and is seen to be paired with the chromomere bands corresponding.
6 and 7. Further contraction of doubled chromatids.
8. A similar stage in the second nucleus from the top, in which the nuclear membrane persists and the nucleus appears as a discrete vesicle.
9. Further contraction of the chromosomes in a well crushed cell.
10. Shown are what appear to be group stages in the separation of the chromatids.
11. Upper cell demonstrates two nuclei in different stages. In the left-hand nucleus the three chromosomes appear as short bars, and in the right-hand nucleus the contraction is complete. The chromatids appear as discrete, paired granules, each pair attached to a small granule here construed as the centromere. The lower cell shows chromosomes in similar stages.
12. Upper nucleus shows three chromosomes on the metaphase plate pulling toward the centrioles. Each chromosome appears double. The upper granule is construed as a mitochondrion.
13. A similar stage. The chromosomes appear as double granules on the metaphase plate.
14. An early anaphase with the chromosomes beginning to pull apart toward the centrioles.
15. A later anaphase stage with the chromosomes migrating toward the centrioles, which are in the axis of the rod. At the right is a mitochondrial granule. In this preparation the wall is stained red, the centrioles and chromosomes blue, and the mitochondrion lavender.
16. Similar anaphase stage in a well crushed cell, showing the chromosomes migrating toward the persistent centrioles.
17. Telophase stage, showing complete separation of the chromosomes and the early reorganization into interphase nuclei.
18. Bacterial rods stained with a double stain in which the cell walls are red, the nucleus and its divisional mechanism blue. The early transverse walls appear as collars derived from the inner surface of the membrane which constrict toward the center with a persistent protoplasmic connection between the dividing cells. This is clearly demonstrated in the upper cell of the upper rod. The uppermost nucleus is in anaphase stage of division. The upper centriole is in focus.

(Plate courtesy of Dr. Edward D. DeLamater. Original work in part in press in *International Review of Cytology*, volume 2, 1953.

biologic prophylaxis and therapy based on immune mechanisms.

The first widely successful chemotherapy of bacterial infections, that with sulfonamides, indeed has only a relatively narrow margin between therapeutic effectiveness and toxicity. Analysis of the mechanism of sulfonamide action has come to focus on reactions concerned with the synthesis and function of certain folic acid-like derivatives of para-aminobenzoic acid.[30] These syntheses and functions seem to be shared by both animal and bacterial cells.

It is perhaps not surprising, then, that the most selective and specific chemotherapeutic agents yet discovered, the antibiotics, should be metabolic products of micro-organisms themselves. It should be a source of chagrin to those associated with medicine that in no single instance has the mechanism of action of an antibiotic been worked out satisfactorily, and that the effort and money directed toward analysis of such mechanisms are still comparatively trivial.

The physician's intervention, in addition to being empiric, suffers severe limitation through the extreme adaptiveness of the microparasites. "In New York City, for example, the proportion of cures of gonorrhea achieved with sulfonamides dropped from about 90 per cent in 1936 to about 30 per cent in 1942. . . . At present, a similar spread of penicillin-resistant staphylococci, and to a much smaller extent of streptomycin-resistant tubercle bacilli, appears to be taking place."[30] Therapeutic successes with the "miracle drugs," even used on an empiric basis, should not obscure the need for rational analysis of mechanisms of action, or for using all the help that laboratory medicine might afford in dealing with such mutable and adaptive organisms as the evolution of the microparasite has enabled them to become.

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Medical Management of Acute Myocardial Infarction and Chronic Coronary Artery Disease

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Increasing use of electrocardiography has led to more rapid and exact diagnosis of acute myocardial infarction. Therapeutic measures, including dosage schedules of preferred drugs, are outlined. Complications which may occur are discussed and treatment for these indicated.

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THE diagnosis of acute myocardial infarction is so well understood these days that even the smallest lesions are being detected. The reason, no doubt, lies in the spreading use of electrocardiography and especially in the knowledge that serial electrocardiograms are of diagnostic importance. Hardly anyone has a chest pain without having two or three tracings taken to determine if any change suggestive of myocardial injury has taken place.

Initially, the object of treatment is to make the patient comfortable. Nitroglycerin usually fails to relieve pain completely. It is generally best to give sufficient morphine for this purpose. Standard practice is to give ¼ gr. of morphine sulfate hypodermically, instructing the nurse to repeat this every half hour until comfort is achieved. On rare occasions, the pain is so excruciating as to justify giving ¼ gr. of morphine sulfate slowly by vein. Of course, there is the usual concern that too much morphine may depress vital centers at a time when cardiac output and blood pressure are depressed by reason of the myocardial infarct. We feel, however, that there is little choice, since a sufficient amount of the drug should be given to obtain relief. So often the patient says, "The pain is killing me, Doc," and we believe that it might if it is not relieved.

We think oxygen by a mask or, preferably, an oxygen tent is helpful in relieving the distress. This is especially so if cyanosis and dyspnea are associated findings. However, many people are apprehensive about oxygen tents and perhaps become excited by them. Good judgment is required under these circumstances to determine if it is worth while.

The secondary shock which may soon develop is a serious complication. If the systolic pressure falls below 80 mm. of mercury, it is a grave prognostic sign and is often associated with a large myocardial lesion. At first the patient should be at complete rest. Small

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plasma or whole blood transfusions (250 cc.) are occasionally administered and even repeated in a few hours if necessary. Pulmonary edema is a potential hazard with intravenous therapy, but if the transfusion is administered slowly, it may be safe. Caffeine and sodium benzoate (7½ gr.) intramuscularly is an old remedy not completely without merit. ADRENALIN® and ephedrine, as well as other pressor amines, also may be tried but, as mentioned before, the development of severe hypotension is a grave sign and only a few survive despite heroic and desperate measures.

We do not use quinidine sulfate (3 or 6 gr. every six hours) or pronestyl (250 or 500 mg. every four hours) routinely. There is much persuasive argument to support such an approach, but we wait and withhold these drugs unless premature contractions appear. We do not hesitate to use them if signs of cardiac irritability develop. Searching for such evidence is certainly one of the real responsibilities of the attending or house physician. Certainly, premature contractions often precede the dreaded ventricular tachycardia or ventricular fibrillation. If such complications occur, the use of pronestyl or quinidine intravenously is often lifesaving. Digitalis is indicated in the presence of auricular fibrillation, in paroxysmal cardiac dyspnea and in congestive failure.

In paroxysmal cardiac dyspnea, or so-called cardiac asthma, the attacks occur usually at night due to congestion in the pulmonary vessels. The vital capacity of the lungs is diminished and the patient awakens in acute respiratory distress. Sitting up seems to help the patient a great deal. Morphine intravenously is most important and when true pulmonary edema is present, a rapidly acting digitalis preparation is necessary. Rather than ouabain, we have used DIGALEN®, 4 cat units, intravenously. This may be followed by an oral preparation the next day, until such time as digitalization is considered complete. Most of these patients require a maintenance dose of 1½ gr., more or less, for the rest of their lives. In addition to digitalization, a low sodium diet and, occasionally, mercurial diuretics are found necessary.

The complications, or sequelae, of myocardial infarctions are often surprisingly few. However, angina pectoris and myocardial insufficiency are the most frequent. Angina pectoris is a paroxysmal type of pain or discomfort in the chest which is induced by exertion or emotion and relieved promptly, usually by rest or termination of the emotional episode. The pain usually begins in the substernal region and may radiate in a circular fashion to ultimately include both shoulders and both arms. However, it may have many atypical sites of origin. Quite a few patients are known to have the pain originate in the elbows or in the jaw. So often, the patient learns that he cannot walk immediately after eating without getting the pain. Under such circumstances, a nitroglycerin tablet beneath the tongue may be of considerable aid as he rises from the table. Preparations such as PURITAL®* or PUROBARB®*, which are essentially purine derivatives, are helpful to some patients if taken three or four times daily. However, the best drug that we have available, and which is too often used insufficiently, is nitroglycerin. Very often the 1/200 gr. tablet is as satisfactory as the 1/100 gr. and has less undesirable side effects. Many people are afraid to take this drug because of the pounding headache which often follows its use, and also because of the skull and cross bones which appear on the label. The patient believes that nitroglycerin, being an explosive, has an explosive effect on him, and this is especially true when he has the pounding headache following its use. However, it is a great comfort to millions of patients to know that they have nitroglycerin tablets in their pockets and to know that the good effects of this drug are rarely, if ever, lost. They never develop tolerance to nitroglycerin, and 1/200 gr. will relieve a pain of similar magnitude next year as well as this. The patient should learn to use the drug prophylactically, i.e., to take a tablet before doing those things which ordinarily induce the pain. Of course it is perfectly safe to take 20 to 25 tablets of 1/100 gr. or 1/200 gr. of

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nitroglycerin daily, repeating them, if necessary, within four or five minutes.

Studies by the American Heart Association in reference to anticoagulants, performed several years ago, have led to the almost universal use of these drugs in acute myocardial infarction and, in the hands of many, in angina pectoris and other conditions. Opinion as to their efficacy varies considerably among many clinicians. Dr. Russeck and others in New York feel that in "good risk" patients these drugs are unnecessary and may be harmful. Other physicians believe they should be used in all cases, as it is difficult to tell when a "good risk" patient may become a "bad risk" patient. There are still other physicians who believe that these drugs should be used only if complications, such as thrombophlebitis or pulmonary embolism, develop in the course of convalescence from a myocardial infarction. We do not believe that there is any rigid means of selecting patients for this treatment. We do not believe it is applicable to all patients as it may be better to treat a patient at home, especially if he is not very ill and if hospital expense and hospital routine would be a real financial difficulty for him. It is certainly true that when the hospital benefits from anticoagulant therapy are explained to many individuals and they reject it, the results of home treatment appear to be just as satisfactory. We think the potential desirability of this treatment in the so-called "good risk" patient is of such doubtful value that after presenting to the patient the possibilities of anticoagulant therapy in a hospital, it is certainly not worth while to insist that he carry it out against his will. On the other hand, in the older subject whose circulatory system is complicated by hypertension, diabetes and other diseases, it seems a reasonable thing to do all that is possible with anticoagulant therapy to prevent venous thrombosis and fatal pulmonary emboli.

Anticoagulant therapy is usually carried on with DICUMAROL® or tromexan. There seems little need to start it immediately or before the third or fourth day of the illness—until one is positive of the diagnosis. One feels rather ridiculous having given anticoagulant therapy to someone with a dissecting aneurysm of the aorta. The therapy requires a daily prothrombin time, which is expensive. The dosage of the drug, or drugs, varies from day to day, depending on the prothrombin time on that day. This treatment is usually carried on for four to six weeks and perhaps longer. Dr. Nichol of Miami suggests its continued use while the patient is ambulant for as long as five or six years, his thought being that the use of this drug will prevent further thrombosis and further coronary occlusions. It is difficult to manage the drug in many patients after they leave the hospital, although it is possible in a few who pay strict attention to the rules and details that are required.

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Diagnostic and Therapeutic Uses of Intestinal Intubation

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Intubation of the intestine is widely employed in the clinical management of patients. In this article are discussed some of the more important applications of this procedure in the diagnosis and treatment of intestinal, biliary and pancreatic diseases.

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INTUBATION procedures have been used for a number of years in the study of the functions and diseases of the alimentary tract. In this country, Einhorn[1] was among the first to intubate the human intestine. In 1931 the use of a distensible balloon fitted onto a tube for the purpose of securing passage of the latter through the small bowel for the study of pain reference was reported by Jones and Pierce.[2] Three years later Miller and Abbott[3] of this clinic published their description of a two lumen tube, providing a means of injecting materials into and aspirating contents from various levels of the bowel. Tremendous impetus to the ready use of intubation resulted and since that date the Miller-Abbott tube and its various modifications have been employed widely in the study, diagnosis and treatment of intestinal disorders. No attempt is made in this report to describe the valuable physiologic and pharmacologic data which have been obtained from experimental applications, but a brief review will be made of some of the more important diagnostic and therapeutic uses to which the original technic and other intestinal intubation procedures have been applied.

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Diagnostic Uses

1. *Biliary drainage*—Lyon[4] has popularized intubation of the duodenum to obtain specimens of bile as an aid in the diagnosis of cholelithiasis. For this purpose a single-lumen tube may be used or a double-lumen one of the type described by Abbott and Rawson,[5] permitting gastric drainage through the second set of openings and yielding a clearer duodenal aspirate, not contaminated with gastric juice. A sample of duodenal fluid is secured and the gallbladder is then stimulated with magnesium sulfate or olive oil to obtain the darker "gallbladder" or "B" bile. The sediment of both specimens is examined microscopically. Cholesterol and/or calcium bilirubinate crystals are found in about 83 per cent of cases of cholelithiasis.[6] If, in addition to these criteria, one adds the repeated failure to obtain "B" bile, duodenal drainage assumes an accuracy of 90 to 98 per cent in the diagnosis.[6,7] It must be emphasized that more than one drainage may be required to reach this degree of precision.

With the present excellence of cholecystographic technics biliary drainage finds its

chief importance in the study of patients with a nonvisualized gallbladder and atypical symptoms and in those suspected of having choledocholithiasis following cholecystectomy, or in association with obstructive jaundice.

This intubation procedure has in addition proved of considerable assistance in the diagnosis of duodenal and biliary parasitism (such as giardiasis and strongyloidiasis) by microscopic demonstration of ova or adult forms. Bacteriologic study of the duodenal aspirate has also been of aid in the study of the typhoid carrier through demonstration of the gallbladder as a reservoir for chronic infection.

2. *Pancreatic drainage*—A double-lumen tube of the Abbott-Rawson type is positioned fluoroscopically in the duodenum, with the proximal openings in the stomach. This arrangement permits aspiration of the duodenal contents without gastric contamination (Figure 1). Duodenal fluid is collected in a chilled container under oil for a given control period and then the pancreas is stimulated by means of an injection of secretin, MECHOLYL® or URECOLINE® and several more duodenal collections of equal duration are obtained. The intestinal specimens can then be quantitated as to volume, *p*H, bicarbonate and enzyme concentrations (amylase, trypsin, lipase). A normal response consists of increases in the first three factors with an elevation in either the concentration or total output of enzymes depending on the stimulant used.[8-10]

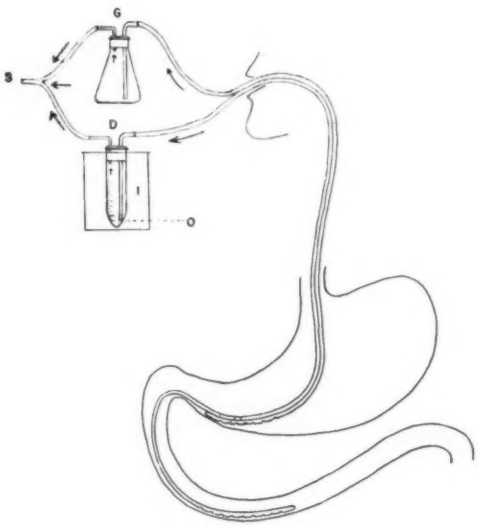

FIGURE 1. Arrangement for pancreatic drainage. Suction (S) is applied to both lumens. Gastric aspirate is collected at G and duodenal aspirate at D, in an iced container (I) under oil (O).

To date most information has been accumulated concerning the response to secretin and various abnormalities of the pancreas and biliary system have, at times, been associated with abnormal results. Thus patients with chronic pancreatitis frequently exhibit an unusually low response to stimulation. The results in carcinoma of the pancreas depend on the location of the tumor, destruction of acinar tissue, and blockage of excretory ducts, but, especially in tumors of the head and body of the organ, the test is sometimes of considerable diagnostic aid. For the differentiation of pancreatic steatorrhea and idiopathic sprue the procedure is quite reliable, a diminished response being characteristic of the former and normal findings the rule in the latter. In the patient with obstructive jaundice diminished pancreatic response implies neoplasm of the head of the pancreas or, more rarely, calculous obstruction of the ampulla of Vater, while normal results indicate a lesion of the biliary system.

3. *Collection of exfoliated cells for Papanicolaou stain*—In the intestinal tract the study of exfoliated cells for the diagnosis of malignancy has been applied principally to the duodenum. Normally the sediment of fluid aspirated after duodenal intubation contains few cellular elements, favoring the identification of malignant cells when they occur. Lemon and Byrnes[11,12] have found this technic quite promising in the diagnosis of certain periduodenal malignancies such as carcinoma of the gallbladder, of the extrahepatic biliary tract, and of the exocrine portion of the pancreas. They report the recovery of malignant cells from nearly two-thirds of such cases studied, with only 1 per cent false positive results.

4. *Diagnosis of site of intestinal bleeding*—

Roentgen examination of the small intestine in cases of bleeding lesions such as a small tumor or a Meckel's diverticulum frequently fails to reveal the site of hemorrhage. In such instances continuous aspiration from the end of a Miller-Abbott tube as it is fluoroscopically observed during passage through the bowel of the actively bleeding patient may serve to localize the source of hemorrhage and guide the surgeon if operative intervention becomes necessary.

5. *Evaluation of recurrent intestinal obstruction*—Patients are not infrequently seen who, perhaps after one or more abdominal operations, complain of recurrent bouts of cramplike abdominal pain. The differentiation of intermittent intestinal obstruction and functional derangement of the bowel (such as irritable colon) is posed. Intestinal intubation may be of aid. If it is found that the distended balloon of a Miller-Abbott tube can successfully traverse the entire small intestine, significant obstruction of that organ is practically eliminated, especially if the patient is having symptoms at the time.

6. *Aid in roentgen visualization of small bowel lesions*—Small bowel tumors, cysts, polyps, etc. are often difficult to demonstrate satisfactorily on ordinary intestinal x-rays. Intubation with the Miller-Abbott tube may assist in the better definition of such lesions.[13,14] If the site of the lesion is known the tube may be passed distal to it, the balloon inflated sufficiently to occlude the intestinal lumen, and thin barium injected through the aspiration holes. This serves to localize the barium to the area in question, prevents filling of overlying loops, and may sufficiently distend the involved segment to permit the taking of diagnostic roentgenograms. Such a technic has been applied chiefly to the duodenum, permitting better definition of the first and second portions and lesions contained therein. The demonstration of a duodenal enteric cyst by such a procedure is shown in Figure 2.

In the search for a lesion producing obstruction, the tube is passed to the obstructed site, barium introduced, and films made in an attempt to discern the nature of the lesion.

FIGURE 2. Duodenal enteric cyst demonstrated with the aid of intestinal intubation. (From Lorber and Machella. *Gastroenterology*, vol. 10. Reproduced courtesy of Williams & Wilkins, Baltimore.)

Since only a small amount of barium need be used and since it can be aspirated readily, there is little need to fear impaction as is the case following a barium meal.

Lorber and Shay[15] have devised a procedure for better roentgen examination of the afferent loop and stoma of patients who have been subjected to gastroenterostomy following subtotal gastrectomy. By blocking the efferent loop with a distended balloon, orally administered barium flows more readily into the afferent intestine allowing visualization of contained lesions.

7. *Aid in cholangiography*—One of the principal causes of persistent or recurrent jaundice and/or pain following cholecystectomy for cholelithiasis is residual biliary tract stone. The search for such lesions in the patient in whom a T tube has been left in the common bile duct includes attempted roentgen visualization of the calculus following the injection of a contrast medium into the ducts through the tube. Fairly often, however, the medium fails properly to fill the biliary tree, flows out into the duodenum, and renders definition of residual calculi impossible. To

circumvent this, Miller, Blakemore and Tondreau[16] have recently experimented with occlusion of the ampulla of Vater during the performance of cholangiography by means of a distended balloon introduced into the second portion of the duodenum. Their results have been most encouraging and they have collected several cases in which their procedure has permitted roentgen demonstration of biliary tract lesions whereas previous attempts at visualization without balloon occlusion had been unsuccessful. One such case is illustrated in Figure 3 and shows the excellent demonstration of biliary duct calculi possible with this technic.

8. *Simulation of pain arising from the intestinal tract*—Not infrequently one encounters patients with functional or organic disease of the gastrointestinal tract in whom the location of pain is unusual and raises a question of reference from the alimentary canal. Thus, Machella, Dworken and Biel[17] have studied a series of patients with the "splenic flexure syndrome" in whom gaseous distention of that portion of the colon was associated with precordial and left arm pain suggestive of cardiac disease. By distending a balloon in the splenic flexure following retrograde intubation of the colon through a sigmoidoscope they were able to reproduce faithfully the extra-abdominal pain distribution of which their subjects complained.[18] Several of their patients had been under treatment for presumed cardiac disease before this procedure demonstrated the intestinal origin of their symptoms. While to the present time used chiefly for investigative study of pain reference, there is no reason why such a simple technic may not occasionally be most helpful in arriving at a correct diagnosis in patients with gastrointestinal complaints presenting bizarre pain patterns.

Therapeutic Uses

1. *Intestinal obstruction*—The prime therapeutic indication for use of the Miller-Abbott tube is in the treatment of intestinal obstruction. Since the turn of the century the mortality rate from all types of mechanical obstruction of the small bowel has declined from about 60 per cent to less than 10 per cent.[19] Improvement in preoperative and postoperative care and surgical technic, and increased knowledge of fluid and electrolyte disturbances, as well as bowel decompression by intubation, have been largely responsible for this achievement.

Intestinal distention by gas and fluid is a feature of either mechanical or paralytic obstruction and, of itself, exerts deleterious effects. Compression of intramural blood vessels may occur producing a strangulating effect and gangrene of the bowel. In mechanical obstructions moderate distention serves to stimulate peristalsis

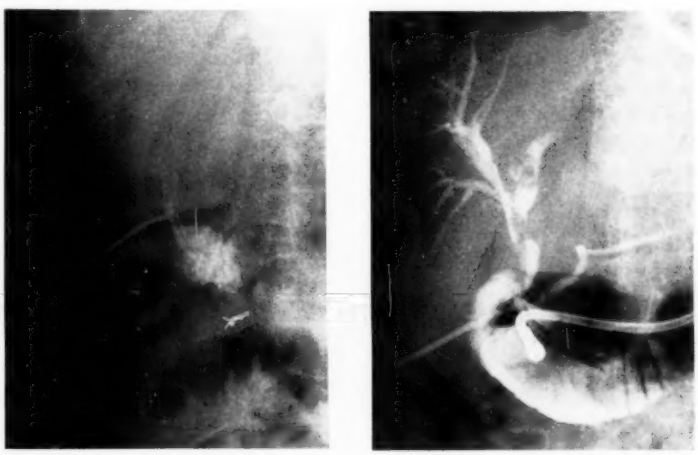

FIGURE 3*a*. Attempted cholangiogram through T tube unsuccessful; contrast medium flows into duodenum. *b*. Same patient. Occlusion of ampulla of Vater by balloon permits filling of biliary system through T tube and reveals calculus in left hepatic duct. Note filling of pancreatic duct. (From Miller, Blakemore and Tondreau. *Surgery*, vol. 33. Reproduced courtesy of The C. V. Mosby Company, St. Louis.)

(somewhat analogous to the effect of increased diastolic filling on ventricular contraction) while overdistention tends to reduce the peristaltic activity and to add the features of paralytic ileus to already existing difficulties. In addition, intestinal distention may contribute to pathologic changes in the absorptive capacity of the mucosa and, by its mechanical effect, induces respiratory and cardiac embarrassment. Relief of distention, therefore, remains one of the primary aims in the management of the patient with obstruction and is best accomplished today by intubation. At times the improvement induced, together with that derived from fluid and electrolyte replacement, may serve to circumvent the necessity for surgical intervention. If operation becomes necessary the patient and his bowel are in much better condition to tolerate it. In paralytic ileus symptoms and signs may be relieved until normal peristalsis returns. West and Schetlin[19] have recently reported on 131 cases of acute mechanical small bowel obstruction treated without intubation and with 20 deaths or a mortality rate of 15.2 per cent. By contrast, in 40 patients who were intubated there were only 3 deaths or 7.5 per cent mortality.

2. *Protection of intestinal anastomoses*—Distention of the bowel in the region of an anastomosis may produce rupture of sutures and leakage of intestinal contents. Decompression by means of a proximally placed tube serves to prevent this. In intestinal operations the Miller-Abbott tube is suitable for this purpose. For the care of a gastroenterostomy Abbott and Rawson[5] have designed a special short two lumen tube, the proximal fenestrations being placed in the stomach and used for aspiration of the acid gastric juice while the distal openings are located in the intestine beyond the stoma and may be employed for administration of liquid feedings. The tube is put in place at the time of operation.

3. *Treatment of intestinal parasitoses*—One of the prime requisites for the successful treatment of most intestinal parasites is that an effective drug be brought into intimate contact with them in as high a concentration as possible. Many of the vermifuges and vermicides are unpleasant to take orally, especially for children. For these reasons many physicians prefer the intraduodenal administration of such drugs. *Aspidium* oleoresin is frequently used in this manner for the therapy of *Taenia saginata, T. solium, Diphyllobothrium latum* and *Hymenolepis nana parasitoses.*

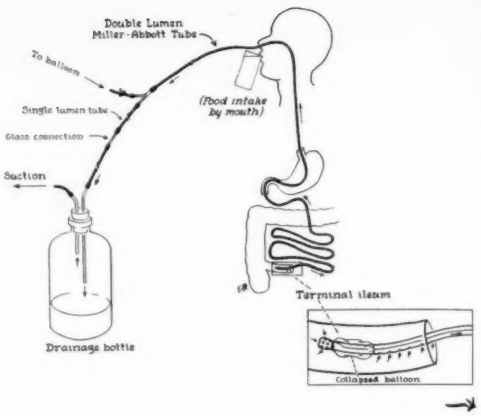

FIGURE 4. Miller-Abbott tube positioned in terminal ileum for "medical ileostomy." (From Machella and Miller. *Gastroenterology*, vol. 10. Reproduced courtesy of Williams & Wilkins, Baltimore.)

4. *Medical ileostomy*—In chronic ulcerative colitis diversion of the fecal stream from the involved colon by ileostomy often results in symptomatic and organic improvement. Machella and Miller[20] have described an ingenious intubation procedure for attempting to secure such results without the necessity for surgery. A Miller-Abbott tube is passed to the terminal ileum, or proximal to diseased bowel, and maintained in this position for as long as several weeks (Figure 4). The ileal contents are continuously aspirated to prevent access to the affected mucosa. Nutrition is maintained orally with a liquid mixture of casein digest and DEXTRI-MALTOSE® or other low residue foods, supplemented with essential vitamins and iron. By use of this technic Machella and Miller were able to induce a remission in 11 of 12 patients for varying periods of time. In 2 patients who relapsed remission was again induced following reinstitution of the procedure. Anton and Secrest[21] have confirmed the beneficial effect of "medical ileostomy" and have reported a patient in whom its use seemed to be lifesaving.

5. *Prevention of intestinal obstruction from adhesions*—Dworken, Miller and Machella[22] recently reported the use of the Miller-Abbott tube in a novel attempt to prevent obstruction of the small bowel as a result of postoperative intestinal adhesions. Their patient had had an ileostomy and colectomy because of ulcerative colitis. Frequently recurring obstruction necessitated numerous surgical operations for lysis of dense adhesions. Following the last such procedure, a stiff, size 18 French Miller-Abbott tube was passed through the bowel, the proximal end being brought out through a gastrostomy (Figure 5). The tube was left in position for three weeks and it was hoped that the presence of the tube in the intestinal lumen might hold the loops of bowel sufficiently separated to prevent recurrence of obstructing adhesions. To date, the patient has not required further surgical intervention in a 10 month follow-up period.

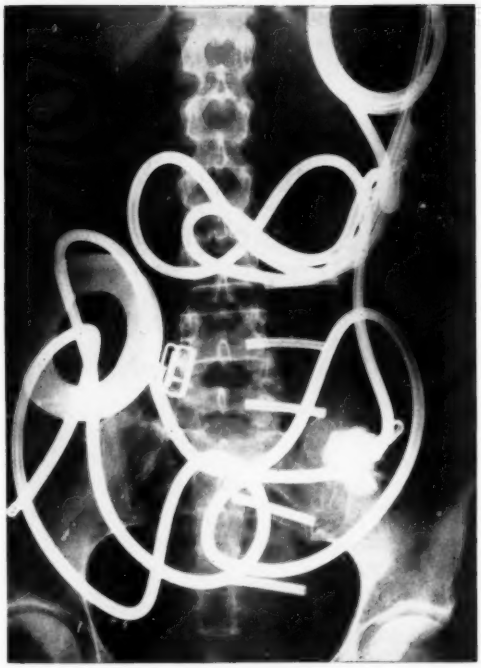

FIGURE 5. Use of Miller-Abbott tube postoperatively to prevent obstruction from adhesions. Distal end of tube passes through ileostomy and proximal end is brought out through gastrostomy.

Summary

The impetus given to the use of intestinal intubation by the researches of Miller and Abbott and others has resulted in a widespread use of such procedures for the diagnosis, treatment and study of alimentary tract disease. A few of the more important clinical applications of intubation technics have been reviewed in this article. It is most probable that the future will reveal numerous new uses for this method of approach.

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Current Therapy in Essential Hypertension

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Careful clinical evaluation, together with a few simple laboratory tests, is essential before undertaking the treatment of essential hypertension. The follow-up of the patient, including selective laboratory studies, is equally important to note any progression of the disease. These points are stressed in the light of therapy with hypotensive agents which are in current use.

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THE varied and intricate concepts concerning the pathogenesis and treatment of essential and malignant hypertension cannot be expressed in this article; an excellent report on the former has been written by Page.[1] We shall attempt to review briefly the treatment of this disease, which has become somewhat more complex with the recent addition of several new drugs to the medical armamentarium. Only brief mention will be made of sympathectomy and adrenalectomy. Pheochromocytoma, congenital cardiovascular lesions, and organic urinary tract disease such as polycystic disease, infections, etc., which constitute about 10 per cent of cases of hypertension, will not be discussed. The remaining 90 per cent, that group known as essential hypertension, are those in which the elevation of blood pressure results from an interplay of many factors primarily affecting the arteriolar tone.

The exact etiology of essential hypertension remains obscure, and the choice of treatment may vary from time to time and from patient to patient. Thus it is essential to emphasize the importance of several initial studies which should be undertaken to evaluate an individual patient properly. With few exceptions these may be performed on an ambulatory patient. They should include, in addition to the history and physical examination, the lying and standing blood pressure readings, evaluation of the ocular fundi, urinalysis, phenolsulfonphthalein (PSP) test, dilution-concentration tests, electrocardiogram and chest roentgenogram. SODIUM AMYTAL® and cold pressor tests are also desirable. A blood urea nitrogen and urea clearance test may also be of value, particularly if there is indication of renal insufficiency.

Jeffers[2] believes that patients with markedly lowered standing blood pressures are not candidates for surgery or sympathicolytic drugs. The PSP test should be repeated, together with other tests if necessary, at approxi-

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TABLE 1

NUMERICAL VALUE OF VARIOUS FACTORS WHICH INFLUENCE PROGNOSIS IN HYPERTENSION

FACTOR	NUMERICAL VALUE
Cerebrovascular accident with or without minor residual Abnormal electrocardiogram Enlarged heart Impending heart failure Phenolsulfonphthalein excretion less than 25 per cent in 15 minutes or less than 60 per cent in two hours Age 50 years or older Mild angina	1
Cerebrovascular accident with residual* Frank congestive failure; moderate angina Phenolsulfonphthalein excretion less than 20 per cent in 15 minutes Unsatisfactory response to sedation	2
Phenolsulfonphthalein excretion less than 15 per cent in 15 minutes	3
Nitrogen retention	4

*Cerebral deterioration or hemiparesis.

TABLE 2

CLASSIFICATION OF HYPERTENSIVE PATIENTS ACCORDING TO THE CRITERIA OF SMITHWICK

GROUP	NUMERICAL GRADE	OTHER FACTORS
1	Less than 4	Eyegrounds grade 0 or 1 (male and female) Eyegrounds grade 2 or 4 (female)
2	Less than 4	Eyegrounds grade 2, 3 or 4 (male) Eyegrounds grade 3 (female)
3	4 or more	Resting diastolic level below 140 mm. Changes present in cerebral, cardiac and/or renal areas, but not including the following: 1. Cerebrovascular accident with marked residual 2. Frank congestive failure 3. Phenolsulfonphthalein less than 15 per cent in 15 minutes associated with poor response to sedation
4	4 or more	Resting diastolic pressure below 140 mm., combined with one or more of the following: 1. Cerebrovascular accident with marked residual 2. Frank congestive failure 3. Phenolsulfonphthalein less than 15 per cent in 15 minutes combined with poor response to sedation Resting diastolic level of 140 mm. or more

mately six month intervals to attempt to evaluate any progression of the disease process which may necessitate a change in therapy. Hafkenshiel[3] is of the opinion that if the percentage of PSP excreted in 15 minutes is less than 15 per cent, it is unlikely that permanent benefit will be obtained from our present methods of treatment.

After these studies have been carried out, the type of therapy to be employed should be considered. Will the individual need only observation and perhaps mild sedation; are depressor drugs and/or diet indicated, or should surgery be considered?

Let us first consider mild hypertension, mainly systolic in character. This is the type of hypertensive cardiovascular disease usually found in patients of the middle and older age groups with few symptoms attributable to their disease—Smithwick's[4] group 1 (Tables 1 and 2). Arteriosclerosis is frequently an associated finding. Because of the relatively benign nature of their disease with slow progression, these patients rarely need more active therapy than mild sedation, reassurance, observation and weight reduction if necessary. It may be mentioned that arteriosclerosis, particularly renal arteriolar sclerosis, does not necessarily antedate hypertension; Castleman and Smithwick[5] found moderate to severe vascular changes in only 55 per cent of 500 renal biopsies performed on hypertensive patients.

The remaining patients with moderate to severe hypertension, Smithwick's[4] groups 2, 3 and 4, are candidates for more vigorous therapy. Among these are patients with too much renal damage to be suitable candidates for surgery, those with so-called "poor" surgical results in whom further attempts at lowering the blood pressure are made, and those

who eventually may be candidates for surgery, depending especially on the progression of their disease.

Evaluation of Drugs

The problem of evaluating the newer drugs now available for the treatment of hypertension is exceedingly complex. Not enough time has elapsed for their complete appraisal—their effect over a long period of time and, perhaps more pertinent at present, their effect on the ambulatory patient as seen in practice rather than under controlled hospital conditions with bed rest, diet, change in environment, etc. It is to be emphasized, however, that all patients with hypertensive cardiovascular disease who are overweight are placed on a weight reduction diet at the start of any program of therapy.

The first drug to be mentioned is potassium thiocyanate. This drug has as its main virtue that of relieving the hypertensive headache. The blood thiocyanate level should be checked at regular intervals and kept approximately between 4 and 6 mg. Pines and Perera[6] recently found that the administration of thiocyanate may cause a sodium diuresis, and expressed the belief that this may explain, at least in part, its hypotensive action.

Certain of the newer drugs exert a depressor action presumably due to their effect on the brain. These include the *Veratrum* alkaloids and the combination of dihydrogenated ergot derivatives (HYDERGIN®), which also produce an adrenergic blockade. It is felt that only a limited number of patients with hypertension will respond to the *Veratrum* preparations, and this can be determined only by clinical trial. As will be mentioned, these alkaloids are useful and safe for parenteral use in hypertensive crises. Their disadvantage lies in the proximity of the toxic dose to the therapeutically effective one; severe nausea and vomiting frequently prohibit their use.

The effects of sodium nitroprusside as a hypotensive agent have been studied at the Cleveland Clinic. The long-term effects remain to be evaluated, although Page[7] feels that part of its hypotensive action depends on its conversion in the body to thiocyanate.

The use of various blocking agents in the treatment of essential hypertension has gained increasing popularity. These drugs, having as their main action the blocking of nerve impulses at the autonomic ganglions, include tetraethylammonium chloride, pentamethonium and hexamethonium. Tetraethylammonium chloride is of limited usefulness in the treatment of essential hypertension, since it must be given parenterally and its action is of short duration. The hexamethonium salts are the most potent blocking agents now available and in most widespread use. They may be given parenterally or by mouth. Hexamethonium chloride (the bromide is not recommended for long-term oral use) is available in 250 mg. tablets. The recommended oral dose for patients with moderate to severe hypertension is 125 mg. four times daily before meals and at bedtime. For those on a low salt diet or for sympathectomized patients, *since they are more sensitive to the drug*, 125 mg. once or twice a day is suggested as the initial dose. One-half to one tablet is added with each dose on successive days if no untoward reactions are encountered. It is recommended that a total daily dose of 2 to 3 gm. not be exceeded. The parenteral dosage of hexamethonium is much less than the oral form due to apparent incomplete absorption of the drug when given by mouth. Thus the parenteral dose may vary from 1 to 50 mg. of hexamethonium as compared with 125 to 750 mg. by mouth. The initial parenteral dose should not exceed 1.5 to 3 mg. of hexamethonium ion corresponding to 2 to 4 mg. of hexamethonium chloride. Freis and co-workers[8] have outlined an appropriate schedule and precautions for the parenteral use of hexamethonium. At present, because of the possible undesirable hypotensive effects, this mode of administration is rarely indicated.

Grimson and his associates[9] state that the significant parasympatholytic side effects—dryness of the mouth, constipation and/or diarrhea, blurring of vision, nausea and anorexia—and occurrence of postural hypotension seem to be more reliable guides to the adjustment of the proper oral dosage of hexamethonium than the individual random blood

pressure determinations, since a sudden or pronounced fall in pressure may be undesirable and dangerous in certain patients, especially those with coronary, cerebral or renal insufficiency in whom the resulting reduction in blood supply may be harmful. The initial evaluation of each patient, as mentioned previously, should help to determine those cases in which *extreme caution* must be used in treatment with any of the blocking agents. The patients should also be told of these possible side effects. They are advised to have a bowel movement at least every other day, using laxatives if necessary. In addition to the precautions necessary while administering hexamethonium and many other hypotensive agents, it is also important to realize that their withdrawal, even in combined therapy, should be extremely gradual in order to avoid a sudden elevation of blood pressure. This is especially important in cases of malignant hypertension, in which deaths have been reported apparently secondary to cessation of therapy.

Tolerance to hexamethonium may occur.[8] Combined therapy with other agents, as mentioned later, may forestall this development.

As with the use of potassium thiocyanate or following sympathectomy, hexamethonium may relieve many of the symptoms of the hypertension without significantly affecting the blood pressure. It is to be hoped, but by no means proved, that these drugs or others with similar actions may alter or slow the course of the disease process.

Other blocking agents include the benzodioxanes, regitine and dibenzyline, which produce a peripheral blockade of sympathoadrenal activity. They are used primarily at present for the diagnosis of pheochromocytomas, in preoperative preparation and during the operative procedure. Their combination with other forms of therapy is now being investigated.

Apresoline, 1-hydrazinophthalazine hydrochloride, is another new hypotensive drug and one which apparently acts mainly through central pathways and also has, in large doses, adrenolytic and sympatholytic properties. It is also reported to increase renal blood flow. Apresoline may be given orally or parenterally. The oral dosage may vary from 25 mg. to possibly 200 mg. four times a day, starting with the lower dose and increasing it depending on the individual's response and reaction. Parenteral therapy, again to be used in the hospital and when the drug cannot be taken by mouth, is initiated by giving 20 to 40 mg. intravenously or intramuscularly with frequent blood pressure determinations during the procedure. Further administration is given according to the patient's response, although oral therapy usually can be started within 24 to 48 hours. The possible side effects of apresoline should also be stressed to the patient. These include tachycardia, palpitations, nausea, vomiting, dizziness and headache. The latter may occur shortly after initiation of therapy and usually subsides within 7 to 10 days with continued treatment. Postural hypotension may also occur and the same precautions should be taken in treating patients with known coronary, cerebral and renal ischemia as with hexamethonium.

Tolerance to apresoline has also been reported after prolonged administration.[10] Again, combined therapy may lessen this possibility. When used alone, withdrawal of the drug for a period of a week may overcome this disadvantage.

As stated by Grimson,[9] apresoline's complex action may make it a useful drug in treating toxemia of pregnancy and early malignant hypertension.

Because of the effectiveness of hexamethonium and apresoline in certain patients, and in an attempt to avoid the development of tolerance to either drug, it is only natural for combined therapy to be employed. It is to be emphasized, however, that all investigations to date recommend that this form of therapy be initiated only under hospital supervision. Combination of the other agents previously described is now being investigated and the results of these studies will undoubtedly prove of interest.

Sodium restriction for the treatment of hypertension is now adequately established as a beneficial measure for a significant number of hypertensive patients, and such restriction will relieve symptoms in a much larger group

if properly carried out.[11-14] Unfortunately the required degree of dietary sodium restriction (300 to 500 mg. daily) is seldom attained, and is uncommonly maintained for any great length of time by diet alone because of the difficulty in preparing or obtaining such diets and because of their monotony. Full benefit from sodium restriction can be attained rapidly in some patients but only over a period of months in many others.[11,13,14] Further, most diets containing less than 700 mg. of sodium tend to be nutritionally inadequate. The rice diet[15] is probably the simplest way of attaining the lowest possible sodium intake, but it has the other drawbacks already mentioned.

Cation Exchange Resins

The development of cation exchange resins has introduced a new and helpful, if still short of ideal, method of controlling body sodium,[16] and they have been found to be useful adjuncts to but not substitutes for dietary sodium restriction.[13,17] With their use dietary sodium levels of 1 gm. may be utilized, and the urinary sodium level will remain at or below 500 mg. per 24 hours—the sodium excretion level that must be attained in cases of hypertension before a significant drop in blood pressure is achieved.

The resins which are in common use are RESODEC®, a carboxylic ammonium-potassium resin; CARBO-RESIN®, a carboxylic hydrogen-potassium resin with a small amount of anion exchange resin added to mitigate against acidosis, and KATONIUM®, a sulfonic ammonium-potassium resin. At present there seems to be little difference in their efficiency and the choice among them appears to depend on the patient's individual taste and tolerance. Recently, mixtures of carboxylic and sulfonic resins have been tried as has the combined use of resins and chelating agents, but neither of these devices has given any practical improvement over the resins used singly as ion exchangers.[18] Other materials whose cation exchange properties have been studied, such as alginic acid[19,20] and phosphonic acid,[21] have been found to be inferior exchangers compared with the synthetic resins.

Selection of patients for cation exchange resin therapy should be limited to those with no great loss of renal function as shown by the clinical tests already mentioned in order to avoid severe acidosis, rise in blood urea nitrogen, low salt syndrome or rise or fall in blood potassium. Also, daily rations of 1 gm. of potassium citrate and calcium lactate should be given as a precaution against bodily depletion of these ions by the resins.

TABLE 3

RESULTS OF DIETARY SODIUM RESTRICTION AND CATION EXCHANGE RESIN THERAPY IN 58 PATIENTS WITH HYPERTENSION

RESULT	CASES	
	Number	*Per Cent*
Diastolic blood pressure drop of 20 or more	24	41
Systolic blood pressure drop of 30 or more	24	41
Mean 24 hour urine sodium of 0.5 gm. or less	22	38
Improved by at least one Smithwick group	16 (of 44)	
Became worse by at least one Smithwick group	0	
Permanently removed from study because of electrolyte disturbance	0	
TOTAL	58	

The foregoing precautions along with close attention to individualization of dietary prescription (a feasible procedure at a dietary sodium level of 1 gm.), frequent dietary reviews, frequent checks of the 24 hour urine sodium, and occasional checks of the blood urea nitrogen and carbon dioxide-combining power have brought forth the results shown in Table 3 in a group of 58 ambulatory, nonhospitalized patients under treatment for 7 to 18 months.

As treatment is continued for longer periods, an increasing number of patients will gradually show a response by a drop in blood pressure, loss of symptoms, improvements in electrocardiogram, fundi, phenolsulfonphthalein excretion and ballistocardiographic pattern, and decrease in degree of cardiac

enlargement.[11,17] Not all patients improve in all these functions, and the improvements do not necessarily correlate with a blood pressure response. Symptoms such as headache and nervousness are relieved in a majority of the patients whether or not the blood pressure drops, and if salt is added, unknown to the patient, the symptoms will return and the blood pressure, if it has fallen, will rise.

Some patients who did not respond to thoracolumbar sympathectomy have done quite well on moderate sodium restriction supplemented by resin therapy.[13]

The unpleasant effects of resin administration, such as constipation, anorexia and unpleasant taste, will pass off in six or eight weeks if the patient continues the regimen, and those who have had extremely rigid low sodium diets usually prefer to take the resins in order to have the more palatable 1 to 1.5 gm. sodium diet.

Studies now under way using low sodium programs in conjunction with some of the previously discussed depressor drugs such as apresoline and dibenzyline seem to indicate that additions of rather small doses of these agents may convert some failures of sodium restriction into therapeutic successes. On the other hand, these same low dosage levels of depressor drugs given without sodium restriction are ineffective in lowering blood pressure, indicating that the combined therapy has either additive or synergistic effect.

Sympathectomy should be considered for any patient with essential hypertension. Although at present it remains impossible to predict which patients will definitely benefit from this procedure, serious consideration should be given in cases of those less than 50 years old with moderate to severe hypertension and little evidence of renal insufficiency, in whom medical management is not successful and who show progression of their disease process. The value of the recent operations on the adrenal glands remains to be evaluated. As already mentioned, the use of blocking agents and sodium restriction following sympathectomy is now being investigated.

In acute hypertensive crises, care must be taken not to reduce the blood pressure too rapidly or too drastically, especially in patients with elevated blood urea nitrogen and fluid and electrolyte imbalances. An attempt should be made to correct these abnormalities before vigorous therapy is instituted to reduce the blood pressure. Since nausea and vomiting are early signs of overdosage, VERILOID® intravenously may be useful. Our experience suggests that it may be safe in conjunction with a low salt diet and perhaps resin therapy, when it can be maintained, in cases in which there is no marked azotemia if the patient is conscious or when consciousness is regained. Those who are conscious with more marked azotemia are perhaps best treated initially with sedation and a low salt, low protein or rice diet.[15] Frequent blood urea nitrogen determinations are mandatory when sodium restriction is employed in such instances. Hydergin or, if ineffective, hexamethonium may be used parenterally if necessary, with the precautions previously mentioned, in the unconscious patient without azotemia.

Malignant hypertension requires extremely careful initial evaluation of the patient with frequent follow-ups for evidence of progression of the disease. If azotemia is not marked, a low sodium diet together with resin therapy may be useful. Although reports at the present time are few, cautious use also of hexamethonium alone or in combination with apresoline may also be employed. As previously emphasized, extreme care with cautious reduction of blood pressure levels must be exercised when these agents are given, especially if any degree of renal insufficiency is present, not only because of the ill effects of any sudden or pronounced reduction in blood flow to the kidneys, but also because hexamethonium is excreted chiefly by the kidneys and toxic amounts may accumulate, resulting in serious side effects. Sympathectomy has been employed in cases of malignant hypertension although Page[7] suggests that it be used only early in the disease in young patients. Page has also had considerable experience with the use of pyrogens in the treatment of malignant hypertension.[22] The treatment is necessarily prolonged but Page feels that it may be worthy of trial in certain instances.

Summary

1. A plan for the evaluation and management of the patient with essential hypertension is presented.

2. The use of the various blocking agents with their possible dangers and side effects is discussed. Hexamethonium is the most potent depressor drug in this group. It is emphasized, however, that the utmost care is necessary when any of these drugs is employed, especially for patients with coronary, cerebral or renal insufficiency and those on a low salt diet or after sympathectomy.

3. Veriloid given parenterally is frequently the drug of choice for acute hypertensive crises.

4. The results of sodium restriction and resin therapy in 58 ambulatory patients are given. Long-term therapy of this type has produced encouraging results. Combination therapy with sodium restriction, resins and depressor drugs is now being investigated.

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MEETINGS AND POSTGRADUATE COURSES

Oak Ridge Institute of Nuclear Studies, Special Training Division: Advanced course covering the clinical applications of radioisotopes, September 14-25, limited essentially to physicians who have had clinical experience with radioisotopes. Additional information and application blanks may be obtained from the Special Training Division of the Institute, P. O. Box 117, Oak Ridge, Tennessee.

Duke University, Durham, North Carolina: Third annual course in acarology, the study of ticks and mites, June 10-29, designed to be especially useful to medical and agricultural entomologists. The course stresses identification of various species of mites and ticks, particularly their habits and properties. Dr. George W. Wharton will be in charge.

GENERAL PRACTICE *Review*

This department offers the latest, proved methods for the treatment and management of commonly encountered conditions based on the extensive experience of the physicians who prepare these summaries for POSTGRADUATE MEDICINE.

Office Treatment of the Foot

LEWIS COZEN

Los Angeles, California

Ingrown Toenails

INGROWN toenails are caused by tight socks or by tight shoes which push the skin into the nail, thus starting an inflammatory reaction at the distal corner. If the corner of the toenail is cut so that the skin overlaps the corner, the skin will again be irritated by the nail as it grows out and the skin cannot get out of the way. There are several reasons why ingrown toenails are so likely to occur in adolescent children. Children are more active than adults, and their activity results in more trauma to their toes and a greater amount of perspiration, the moisture thus aiding the progress of infection. Their socks and shoes are apt to be too small because of their growth, and the nail itself may grow more rapidly than the skin at the edge of the nail (eponychium).

To prevent paronychia, all these factors should be kept in mind. Shoes should be large and not misshapen. Socks should also be large, and the feet should be kept dry.

The treatment of ingrown toenails depends on their state when first seen. If seen early when there is merely a little pain, slight redness and tenderness at the nail edge with little or no discharge, treatment may be conservative. This consists of thinning the nail down with a sharp knife or sterile razor blade. The nail then will be pliable and less apt to press into the soft skin at the edges. Neomycin ointment is applied at the edge of the nail three times daily. A small wisp of cotton may be placed under the corner of the nail for additional protection of the skin. The patient is told to replace the cotton after he takes his daily bath and to massage the skin at the corner of the nail with some cold cream to help push the skin away from the nail. One visit is usually enough if the patient obeys instructions. He must, of course, be cautioned not to cut off the corner of the nail but to allow it to grow out beyond the skin. He may keep the nail thin and pliable by judicious paring of its central portion.

If the patient has a frank infection, with pus draining from his toe in some quantity, treatment must be different. Office treatment should not be considered if the circulation of the foot is impaired; this is determined principally by absence of the dorsalis pedis pulse. If circulation is impaired, the patient should be scheduled for a brief period of general anesthesia in the hospital.

If there is no impairment of circulation to the foot, the patient should be judged as to his ability to tolerate the procedure of in-

filtrating for local anesthesia. Should he be apprehensive, it is much wiser to schedule him for a general anesthetic at the hospital than to attempt the office procedure with procaine infiltration. Infiltration is performed proximal to the base and on both sides of the involved toe, the point of the needle traversing the tissue in all planes as the 1 per cent procaine is infiltrated. Through two skin wheals of procaine, infiltration may proceed on both the volar and the dorsal surface of the metatarsal area. One must wait at least 10 minutes before attempting any manipulation of the toenail, to allow adequate anesthetization of this digital nerve block. A few words of caution are not amiss. Do not infiltrate a circle of subcutaneous procaine in the toe itself. Blood supply may be permanently jeopardized by such an injection. For the same reason, do not add any epinephrine to the procaine.

An oblique incision now is made in the skin at the base of the toenail. First, however, one ascertains that anesthesia is satisfactory by pressing the toe with a needle. If analgesia has been achieved, one may proceed with the operation; if not, it will be necessary to infiltrate about 3 cc. of procaine locally into the toe, underneath the toenail, the point of the needle going between the toenail and the toe itself and infiltrating at the base of the nail on the involved side. There is no danger in infiltrating large amounts of procaine so long as the procaine does not encircle or even partially encircle the toe. As soon as the incision is made a large portion of the procaine is released, thus relieving the tension, but there would still be danger of excessive tension if the solution encircled the toe.

After the oblique incision has been made, a pair of sharp-pointed scissors is inserted longitudinally at the desired level, and the portion to be removed is grasped with a hemostat and removed. Now with a knife or a curet, whichever is available, the base of the nail bed that has been excised is scraped for several minutes to remove its matrix. The small incision at the base of the nail need not be sutured.

After the operation, bleeding may be profuse, but this is not dangerous. The patient must be reassured, however. If there is infection on both sides of the nail, the same procedure must be repeated on the other side of the nail. With adequate drainage, as described previously, soaks or postoperative treatment usually is unnecessary. The dressing is not removed for three or four days unless the patient complains of excessive pain. Usually pain is relieved immediately after the operation and the immobilizing dressing is enough to relieve any pain caused by the procedure itself after the analgesic effect has worn off.

The patient should be given a prescription for a small tube of neomycin ointment, and told to apply this ointment when the dressing is removed after three or four days. It should be remembered that soaks macerate the skin, and unless infection is severe they probably do more harm than good. The patient should be told to prevent recurrences by the methods already outlined.

Corns

A corn is hard when it is on the surface of the toe, and soft when it lies between two toes. Both types are caused by excessive pressure over a small area of skin. To prevent corns one must prevent excessive pressure from any cause such as tight shoes or deformity of the toes. When a hard corn is present on a toe, one must look first for any deformities such as hammer toes. If no deformity is present, the patient is told to have his shoes stretched, especially over the site of the corn. The shoemaker can do this with the help of a small thimble attached to a shoe tree. When new shoes are bought they must be longer than those previously worn. A good method of convincing the patient that his shoes are too small is to place the shoe with its sole touching the sole of the foot, the stocking having been removed previously. Overlapping of the foot will usually convince the patient.

If the toe is deformed slightly into a hammer toe position, a simple felt tunnel splint will often be of help. This felt should be applied every morning as the patient dresses.

The sock should be put on the leg in such a manner that the piece of felt is not curled up. Metatarsal arch-raising exercises, to be described later, will stretch the extensor tendons of the toes and also help to correct the deformity. If the hammer toe deformity is moderately severe, attempts may be made to correct it by repeated adhesive strapping as is illustrated. Should the hammer toes be severe and should there be recurrence of painful corns, operative correction in the hospital is indicated. Probably the most satisfactory operation is excision of the bony phalanx which supports the corn.

The patient should not be allowed to leave the doctor's office without having the temporary relief afforded by removal of the painful corn. A sharp sterile Bard-Parker knife is sufficient for this. If the blade is sharp and the corn is removed in layers so that no bleeding occurs, pain will be minimal. Medication to remove the corn medically may be prescribed. A satisfactory prescription, originally from the Merck Manual, is as follows:

Salicylic acid	1.1 gm.
Lactic acid	1.6 cc.
Collodium	8.0 cc.
Collodium flexile	8.0 cc.

Directions: Apply to the corn twice daily for three days; soak corn in hot water after each application.

The patient should be cautioned not to apply this medication on normal skin. It should be placed only on the corn. It is unsafe to apply an escharotic such as this to a foot that has poor blood supply.

Calluses

Calluses form on the plantar surface of the foot and may be the result of excessive pressure on a small circumscribed area. The usual site of a callus is at the head of a metatarsus and the usual cause is abnormal prominence of the metatarsal heads. To prevent metatarsal callosities one need only prevent excessive pressure on the metatarsal heads. Such pressure may be caused by high heels, short shoes, arthritis of the small joints of the foot or fatigued muscles which fail to give adequate support to the metatarsal heads.

Treatment should provide for correction of

FIGURE 1. Felt tunnel for hammer toe.

the cause. Shoe heels should be lowered for women—a college or cuban heel (1½ inches) is the highest permissible height. The shoes should be examined to ascertain whether they are of adequate length; otherwise crowding of the toes with resultant depression of the metatarsal heads takes place.

Next the callus is trimmed in layers in the same manner as a corn. Then a metatarsal pad is applied to remove pressure from the metatarsal heads. If felt is not available, a pad made from gauze dressings may suffice. In making pads of any type the important principle to be borne in mind is that pressure is to be removed from a painful area and placed on one free from pain. A triangular or oval piece of ½ inch felt is cut. The thickness of the felt must be adjusted to the individual arch. The edges are bevelled with a knife or scissors. The felt pad is tentatively placed just posterior to the painful metatarsal head. It should be thick enough so that when the patient is standing, pressure is mainly on the pad and not on the metatarsal heads. The small pyramid of felt is now placed on the sticky side of a short piece of 3 inch adhesive tape, and a similar piece of tape is

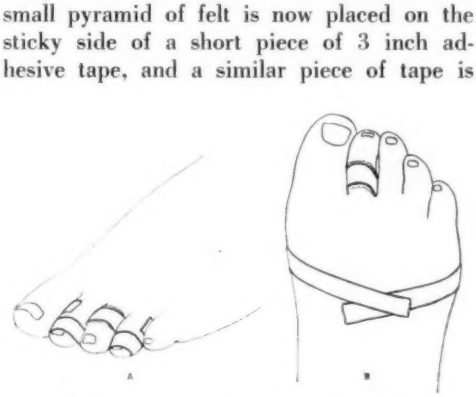

FIGURE 2. Two methods of adhesive strapping to help correct mild hammer toe deformity.

FIGURE 3. Felt pad for metatarsalgia. The felt is sandwiched between two layers of adhesive tape. Both layers of tape have their sticky side facing the foot.

FIGURE 4. The completed strapping, the felt being placed behind the metatarsal heads.

then placed on top of the felt, again with the adhesive side up. Thus the felt is surrounded by tape, yet it can be made to adhere to the plantar surface of the foot so that it will not move from the proper position. Strappings of 2 inch adhesive tape are applied to immobilize the felt pads and the anterior tarsus.

These metatarsal pads should be changed weekly. At the end of one week the felt is compressed and is no longer effective. After three such weekly changes of temporary pads the patient is ready for permanent supports.

Metatarsal supports may be worn inside the shoe or may be in the form of a metatarsal bar. The outside leather bar is usually more effective. In severe cases both internal and external supports are indicated. The bar is placed on the sole of the shoe behind the tender metatarsal heads. It should be ⅛ to ¼ inch thick and thicker for men than for women. It is preferably made by a brace maker, but if none is available, the physician should mark the area for the raise on the sole of the shoe. It is surprising how far back such a bar must be placed to relieve pressure from the metatarsal heads. Shoemakers invariably place the bar too far forward (distal).

The patient is instructed in metatarsal exercises, for example, cupping the metatarsal heads. He is told to grip the ground with his toes and to perform the exercise while standing, walking and sitting throughout as much of the day as possible. Although simple and not difficult to learn, this exercise will give relief in many cases of metatarsal pain.

Treatment for metatarsalgia without callus formation is similar except that there is no necessity for removal of a callus.

Bunions

The cause of bunions has never been adequately established. Probably bunions are a result of shoes that are too small, of stockings that are too short and of heels that are too high. Bunions are seen more frequently in women than in men and this would certainly lend support to the conclusions that footwear is an important, if not the most important, cause of bunions. However, there has been investigation to the effect than an important factor in bunion formation is increased angulation between the first and the second metatarsus.

Bunions are sometimes seen in children, and conservative treatment may be tried in an attempt to correct the hallux valgus deformity. In adults there is no hope of correcting the deformity except by surgery. In children, however, the deformity may be corrected conservatively by their wearing shoes that are large enough—and the shoes must be *large*. To be sure that the size is adequate, the shoe should be measured with its sole against the sole of the foot. There should be room within the outlines of the sole for the entire foot when pressure is placed on the shoe to simulate that of standing. Another method to ascertain whether the size is adequate is to make an outline of the foot and superimpose on it an outline of the shoe. The parent is admonished to be sure that stockings are also large. Following this, the parent is told to teach the child exercises to increase the strength of the adductor hallucis. With both feet flat on the floor, the child brings both great toes together forcibly without moving the rest of the foot—in other words, the great toes are made to pigeon toe forcibly. Next, a night splint of the type that straightens the deformity is ordered. The splint is somewhat uncomfortable and some children will not wear it, but a trial is indicated. During the day the child should wear a post made of sponge rubber between the first and second toes. This post can be procured in most dime stores and in most corrective shoe stores. With

FIGURE 5. Metatarsal bar proximal to the metatarsal heads and a wedge on the inner side of the heel (in white) to tilt the heel into corrected position. The second shoe illustrates an advanced inner border of the heel to give added support to the longitudinal arch. Both the inner wedge and the advanced inner border of the heel may be used together for strain of the longitudinal arch.

such a regimen, it is possible that some correction may take place; at least further progression of the deformity may be stopped.

In adults there is no way to correct the hallux valgus deformity without operation. The only thing that can be done conservatively is to allay the pain of the deformity. If the pain is severe and there is a real bunion as evidenced by a bursitis, either infected or noninfected, it is most important to diminish the pressure on the bunion. This can be done by cutting the slipper or shoe over the area of pressure, by bed rest if necessary and, if infection is present, by the use of antibiotics and warm soaks. If there is merely chronic pain over the bunion, the most important conservative measure is to admonish the patient to change his or her shoes for others that are large enough. One other method is to have the shoe cut at the seam at the base of the sole, the upper part pulled back and then stitched back loosely over the bunion. In this way an old shoe that is not too small may be used. The heel should be low for women, no higher than a cuban or a college heel. If a higher heel is worn, the body weight jams the foot down into the forepart of the shoe, and the tendency for valgus deformity of the great toe is increased. There is only one other measure that may provide relief—to use a flexible plastic or latex appliance that covers the great toe and the area of the bunion. This appliance is built up thickly around the periphery of the tender bunion, thus diverting the pressure to a nontender area around the bunion. An appliance of this type must be made individually by an expert manufacturer. There are not many places where such appliances are made, but they can be found.

Strain of the Longitudinal Arch

In this section we will consider foot strain as applied to the structure on the medial border of the foot, usually called longitudinal arch strain or flat feet. It is frequently difficult to ascertain whether a patient who complains about his feet is suffering from longitudinal arch strain. He may have a rather high arch and still there may be strain, as evidenced by excessive tension on the ligaments and joint capsules of the medial aspect of the foot. True enough, usually the feet are actually flat. Then the heel is everted, the forefoot is abducted, and there is bulging on the inner border of the foot with a lack of longitudinal arch to be observed when the patient stands. Incidentally, flattening of the longitudinal arch is masked when the patient sits. Of course, there must be preliminary examination of the foot to make sure there is no vascular disease or infectious disease such as tuberculosis.

Assuming that no such disease is disclosed, the next procedure is to place the forefinger over the center of the medial border of the foot in the center of the plantar fascia. If this is tender, one can assume that there is longitudinal arch strain; if there is no tenderness, one can assume that no longitudinal arch strain is present even though the feet appear to be quite flat. If tenderness is present, one can make a diagnosis of longitudinal arch strain. The best procedure then is to strap the foot. Adhesive strapping is applied circumferentially around the foot and a pad of felt is placed on the inner border of the foot to conform to the longitudinal arch. The felt edges are shaved down so that they will not press uncomfortably into the skin. The felt should be soft and not very thick, because if it is too thick or too hard, the patient will be too uncomfortable to allow proper test of the support. Probably the support is procured not from the felt but from the adhesive tape, the felt merely preventing the adhesive from becoming too tight and allowing a more even distribution of the adhesive tape by "taking up" the hollow made by the longitudinal arch. Before the strapping is applied, the foot

should be shaved and painted with compound tincture of benzoin. The patient is told to wear this adhesive and felt support for one week. If he attains relief from his symptoms, one may assume that he will be a suitable candidate for an appliance.

The safest appliance to order is a sponge rubber pad, made by an expert orthopedic laboratory, glued into the shoe and covered with a soft leather lining. In addition, a wedge to tilt the heels so that there is less valgus of the heel is ordered. This inner tilt measures 3/16 inch to ½ inch, depending principally on the age of the patient. The younger the patient, the more correction he will take comfortably. In addition, an outer patch to elevate the outer side of the sole should usually be ordered. This amounts to about 3/16 or ¼ inch. The foot is twisted by this elevation so that there is more correction of the longitudinal arch than there would be by simply correcting the heel. Such correction should cost about $3.00 to $3.50 for a pair of shoes. If the patient obtains relief from this correction, one is justified in ordering more expensive supports which will be replaceable and which can be used in any of his shoes. These shoe corrections should be tried for about three to four weeks. Most important in ordering permanent plates or supports that are transferable from one shoe to another is the reliability and the experience of the brace maker. Usually it is best to order a semirigid support made of cork and leather rather than one made of a solid metal such as stainless steel or aluminum. The rigid plastic supports are also usually not as comfortable as the semirigid ones. Again one must insist on choosing the type of support that the brace maker is accustomed to making. At times these supports—especially if they are of solid metal—should be worn for only one or two hours a day. The remainder of the time, the patient carries them in his pocket. The semirigid support, however, may usually be worn continually after a breaking-in period.

There should be no misunderstanding concerning the efficiency of treatment for longitudinal arch strain. For the patient with extremely painful feet, or for the man or woman who must work standing a good part of the day, treatment of any kind will be of no avail. This is particularly true of the patient whose feet are flat and also rigid. Such a patient has, in addition to the excessive strain on the capsule and ligament of the foot, pain as a result of degenerative arthritis of the intertarsal joints of the foot. This arthritis is secondary to congenital limitation of motion of the joints of the foot. With this double handicap, a patient should change his vocation to one which does not require standing. It is indeed rare that such a patient will be able to work with the pain in his feet that gradually becomes extremely severe and finally encompasses his legs, his back and even the upper part of his body. One must be frank with such patients and state the futility of treatment in order to start rehabilitation by change of vocation and also to prevent their spending money uselessly.

Painful Heels

Painful heels in children are caused by an apophysitis of the calcaneus. The child, usually an active boy, will complain of vague pain in the heel. Roentgenograms will show an ununited apophysis of the calcaneus. A film taken of the opposite heel will reveal the same status there. Apparently there occurs some slight infraction at the cartilaginous plate separating the apophysis from the main body of calcaneus. Such a microscopic separation apparently occurs as a result of excessive activity. Treatment consists of raising the heel slightly—about ¼ inch—and, if the pain is in the posterior aspect of the heel, the hard counter of the shoe is removed by the shoemaker.

Another condition that occurs in children, in the heel region, is bursitis of the achilles tendon. The pain in such cases is situated in the posterior part of the heel in the region adjacent to the counter of the shoe. The heel cord usually is irritated by excessive activity of the youngster, and the hard counter rubs up and down on the heel cord with each step. At times there may be actual thickening of the heel cord on both sides. If the thickening extends more proximally, there

FIGURE 6. Tenderness in the center of the plantar fascia, a valuable sign of longitudinal arch strain.

Illustrations are reproduced by permission of Lea & Febiger, Philadelphia, publishers of "Office Orthopedics," by Lewis Cozen, M.D. Ed. 2, 1953.

may be an associated actual tenosynovitis of the achilles tendon. Here again, treatment consists of elevating the heel by placing a pad of sponge rubber or felt inside the heel. This will remove the tender area from the counter so that there will not be recurrent irritation of the heel. The counter itself should be removed by the shoemaker. The area of tenderness should be infiltrated with 3 to 5 cc. of procaine, and a double thickness of adhesive tape should be applied over the tender area, also to prevent irritation. In addition, a piece of felt should be placed in the front of the shoe underneath the tongue. This will give added security to the shoe so that it will not move up and down on the heel with each step.

Painful heels in adults are often difficult to treat. The pain usually is located on the inferior surface of the heel, although it may be more diffuse and located on both sides laterally and medially as well as inferiorly. A roentgenogram will often show a bony spur on the inferior aspect of the heel. Such a condition has been called "lover's heel" because of the supposed relationship to gonorrhea.

The pain is usually caused by periostitis and bursitis of the calcaneus. This periostitis is similar to rheumatoid arthritis, but acts only as a trigger mechanism in the same way that an infection such as a sore throat may be a trigger mechanism for rheumatoid arthritis elsewhere in the body. The presence of a spur is not necessarily indicative of periostitis inasmuch as bony spurs may be present in the opposite foot with no symptoms whatsoever. Treatment should consist first of treating the focus of infection, if there is one, such as gonorrheal urethritis. Next, an arch support should be prescribed to remove weight from the painful heel area. The support should have a hole cut in the center of the heel portion so that there is no pressure placed on the tender area. It is wise to prescribe shoes with sponge rubber heels and soles as they will be more comfortable than shoes with leather or even rubber heels. X-ray treatment to the heel is often helpful, as is cortisone. Cortisone should be tried for a period of about five days in doses of 100 mg. daily. If, at the end of a five day period, there is no relief, the cortisone may be discontinued. BUTAZOLIDIN® is a new drug that should also be tried. It is given in doses of 200 mg. three or four times a day, and it must be given with milk or food in order to prevent gastric disturbances. The well known contraindications for cortisone should be adhered to and the same contraindications apply to butazolidin.

Recently, hydrocortisone has been injected into the periosteum of the os calcis for painful spurs. The skin and subcutaneous tissues are anesthetized with about 5 cc. of 2 per cent procaine. Then, with the aid of a No. 20 needle, 0.75 to 1.0 cc. of hydrocortisone is injected into the periosteum adjacent to the spur. The site of infiltration and injection is the medial aspect of the heel and the needle is directed parallel with the plantar surface of the foot. Usually the injection must be repeated twice weekly for 2 or 3 weeks to relieve the pain.

There has been some association between painful heels and rheumatoid spondylitis, according to Davis and Blair. Therefore, in a severe case, in addition to ordering a sedimentation rate, a roentgenogram of the pelvis may reveal some destruction of the sacroiliac joints indicative of rheumatoid spondylitis. Davis and Blair have reported that radiation of the pelvis offers relief from the painful heels. Surgical excision of the periosteum and plantar exostosis should be done in rare cases and as a last resort. Usually the results of such surgery are unsatisfactory. It should be emphasized to the patient that symptoms of pain will be protracted and that he should not expect relief for a long period of time.

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New Criteria and Management of Essential Hypertension

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IN discussing hypertension, it is essential to define the term as accurately as possible. The criteria hitherto used for the diagnosis of hypertension were ill-defined and loosely applied. Many false diagnoses were therefore made. Patients underwent much unnecessary and misdirected treatment, and became subject to much unnecessary psychologic and physical invalidism. Many people have been told that they had hypertension solely because they had a systolic pressure of 150 mm. of mercury or a diastolic of 90 to 94, and have been treated for it, though they had neither symptom nor sign of cardiovascular disease. In the past these figures were considered abnormal regardless of the age of the patient. Though the blood pressure was known to be lower in the younger age groups, 150/90-94 was accepted as the upper limit of normal in the older age groups as well.

These old criteria of hypertension had come to be accepted as a result of numerous investigations, many of which dealt with relatively small groups of subjects. These included few persons of older age. Insurance company criteria particularly, which have usually been accepted as normal limits of blood pressure, were established as a result of such inadequate studies. To a large extent their subjects were a select younger age group; their figures did not apply to the general population.

It had been apparent for many years that blood pressures above 150 systolic and 90 diastolic were very common in people over the age of 40 years, who usually were in excellent health, active and showed no evidence of cardiac or vascular disease. Occasional blood pressure studies did indicate that the accepted old upper limits of normal were too low. Alvarez[1] and Diehl and Sutherland[2] found that a significant number of normal college students had a systolic pressure above 140. Richter,[3] Saller[4] and Kylin[5] observed that systolic blood pressure increased with age. Saller[4] noted that the systolic pressure in normal men after the age of 68 was sometimes as high as 186 mm. and in normal women as high as 222. Kylin[5] accepted 170 as the upper limit of normal systolic pressure.

Master, Marks and Dack[6] found that the majority of men over 60, and of women over 50, had a systolic pressure of 150 or more and/or a diastolic pressure of 100 or more. Perera and Atchley[7] pointed out that normal,

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TABLE 1

NORMAL RANGE AND LIMITS OF HYPERTENSION

AGE (YEARS)	NORMAL RANGE		HYPERTENSION, LOWER LIMIT	
	Male	*Female*	*Male*	*Female*
	SYSTOLIC			
16	105-135	100-130	145	140
17	105-135	100-130	145	140
18	105-135	100-130	145	140
19	105-140	100-130	150	140
20-24	105-140	100-130	150	140
25-29	108-140	102-130	150	140
30-34	110-145	102-135	155	145
35-39	110-145	105-140	160	150
40-44	110-150	105-150	165	165
45-49	110-155	105-155	170	175
50-54	115-160	110-165	175	180
55-59	115-165	110-170	180	185
60-64	115-170	115-175	190	190
	DIASTOLIC			
16	60-86	60-85	90	90
17	60-86	60-85	90	90
18	60-86	60-85	90	90
19	60-88	60-85	95	90
20-24	62-88	60-85	95	90
25-29	65-90	60-86	96	92
30-34	68-92	60-88	98	95
35-39	68-92	65-90	100	98
40-44	70-94	65-92	100	100
45-49	70-96	65-96	104	105
50-54	70-98	70-100	106	108
55-59	70-98	70-100	108	108
60-64	70-100	70-100	110	110

aged people might have a systolic pressure of 160 to 180 mm. Evans[8] considered 180/110 mm. to be the upper limits of normal. Other authors also stressed the need for raising the normal blood pressure limits.[9-11]

New Criteria

In 1950 Master, Dublin and Marks[12] published their observations on the blood pressure of 74,000 persons, from 16 to 64 years of age, who were in average good health and who worked in industrial plants throughout the country during World War II. The findings are shown in Table 1. The normal range of the systolic and diastolic pressures, as well as the limits beyond which the readings are probably abnormal, is shown for both sexes and for each age group. Between the upper limit of normal and the lower limit of hypertension lie the borderline cases—these may be normal or abnormal. It is in this group, particularly, that a very thorough examination is necessary to establish the diagnosis and evaluate the blood pressure.

It will be seen that the upper limit of normal systolic pressure increases with age and that it is slightly higher among men up to the age of 45, and among women after 45 (Table 1). For example, at the age of 16, the upper limit of normal in men was found to be 135, and the lower limit of hypertension was found to be 145; in women, the corresponding figures were 130 and 140. In the 55 to 59 year age group, however, the upper limit of normal in men was 165 and the lower limit of hypertension was 180; in women, the limits were 170 and 185. The diastolic pressure follows the same trend as the systolic although the rise with age is less marked. At the age of 16 the upper limit of normal was 86 mm. and the lower limit of hypertension was 90; at the age of 64, the corresponding figures were 100 and 110.

To summarize the new criteria: A systolic pressure of 150 to 160 may be normal in a man or woman of 40 to 50, and a systolic pressure of 170 may be normal in a man over 60, and 175 in women over 60. A diastolic pressure of 96 may be normal in people of 45 to 50 and a diastolic pressure of 100 may be normal over the age of 50. In fact, even higher blood pressures than these may also be normal, i.e., those between these upper limits of normal and the definitely hypertensive levels for each age and sex.

These findings have some very practical applications.[13] Thousands of men and women over 45 have blood pressures of 150/96 to 175/100 but feel well and present no evidence of cardiovascular disease. In the past, these people have been labelled hypertensive; yet when their blood pressures are compared with those in the newly established tables, age and sex being considered, it is evident that many fall within the normal range and are not hypertensive. Such asymptomatic patients require neither observation nor treatment, and may be accepted for employment and military service. However, if they suffer from an an-

ginal syndrome, if they have dyspnea or other evidence of congestive failure, or if cardiac enlargement, significant alteration in the electrocardiogram, retinal abnormalities or signs of renal involvement are present, the patients should be considered to have hypertensive disease, despite the finding that their blood pressures are within the new normal limits. It is not the height of the blood pressure, per se, but the symptoms and signs induced thereby, which are of diagnostic significance.

Hypertension and Coronary Disease

The relationship of hypertension to arteriosclerosis, and particularly to coronary disease, has not yet been clearly defined. Because false criteria of normal blood pressure had been employed in the past, it was generally assumed that hypertension was a major cause of coronary sclerosis. Various authors had previously found that "hypertension" was present, prior to the attack, in 40 to 70 per cent of men with coronary occlusion; in women the percentage was as high as 80. It is a well known dictum that women who develop coronary disease are likely to have hypertension or diabetes. Employing the newly established criteria of hypertension, however, the senior author found that only 25 per cent of men with coronary occlusion had previous hypertension, whereas 75 per cent of women had been hypertensive.[14] Thus, men are less apt to develop hypertension; they develop it at an earlier age and they do not require hypertension as a basis for coronary disease. In women, on the contrary, hypertension is more common; it usually occurs after the age of 50 and it precedes coronary disease in 3 out of every 4 cases.

The reason for this difference in the sexes is not known. Possibly, recent observations on blood lipoproteins and cholesterol may explain it. Jones, Gofman and their colleagues[15] found that the Svendberg flotation fraction of the blood, i.e., the S_F 12-20 lipoproteins, rose to the high level of 39 mg. per cent in men at the age of 30 whereas it did not attain this level in women until the age of 55 to 60. Similarly, Russ, Eder and Barr found less plasma beta-lipoprotein in women under 45 than in men.[16] This is also true of serum cholesterol;[15, 17, 18] in men, its peak occurs at the age of 55 whereas in women the peak is not reached until the age of 60 to 70 years.

It was found also that hypertension was associated with increase in the S_F 12-20 lipoprotein fraction,[15] as well as in cholesterol.[19, 20] If one assumes that there is a causal relationship between serum lipoproteins, cholesterol and arteriosclerosis, it follows that women are particularly apt to develop coronary disease after the age of 55 to 60 because these blood elements are then at their highest level.

Much has been written concerning the relationship of the sex hormones to coronary disease and hypertension. On the assumption that the female sex hormone protects women from hypertension and coronary disease until after the menopause, this hormone, as well as testosterone, has been administered to men with angina pectoris. Only occasionally have favorable results been obtained. It has recently been reported that injections of estradiol benzoate inhibit coronary atherogenesis in cholesterol-fed cockerels.[21] It has therefore been suggested that estrogenic function maintains a normal phospholipid-cholesterol ratio in women.

Treatment

If a patient's blood pressure falls within the newly established hypertensive levels, the need for treatment depends on the presence of sclerosis of the coronary, cerebral, renal or retinal arteries, rather than on the degree of the hypertension. When there is no evidence of such involvement, and when no symptoms (e.g., severe headache) are attributable directly to the hypertension, therapy is often not required unless there is a definite progression of the hypertension. Treatment is frequently unnecessary because many people with definite or severe hypertension do not develop any related complications and live as long as nonhypertensives. For example, Bechgaard[22] studied 1000 patients, many of whom had blood pressures over 180/100 and up to 240/130. After 4 to 11 years half of the patients were quite well or

entirely asymptomatic. He found that the excess mortality due to hypertension diminished with advancing age. Burgess[23] observed patients with blood pressures of 130/100 or more for at least eight years. He concluded that the prognosis is usually good in hypertension which has persisted for so long a time and which is not associated with definite cardiac or renal disease.

It is best to tell the patient about his elevated blood pressure because he will probably learn about it sooner or later. If the condition is explained frankly and reassuringly, with emphasis on its usual benign course, the patient accepts it gracefully. If these precautions are not taken many patients develop an anxiety state with many resultant symptoms.

Psychotherapy

It is important to understand the emotional disturbances and the anxiety which beset these people. It has been suggested that many people with essential hypertension have a personality pattern characterized by repressed hostility, unreleased aggression and resultant anxiety. A continued state of conflict exists because hypertensives adapt to the stress of situations by restraining their strong aggressive drives. They maintain peace and win approval at a tremendous price. Wolf and Wolff[24] have shown this type of reaction in hypertensives to result in peripheral vasoconstriction and increased cardiac output. Persons with normal blood pressure, on the contrary, are apt to respond to anxiety by an increase in cardiac output without peripheral vasoconstriction. It has been postulated that permanent vascular changes may appear, when hypertensive patients react repeatedly and intensely with increased peripheral resistance, through the pituitary-adrenal system.

In many cases of hypertension the physician may apply simple psychotherapy with good results. A complete personality change may never be achieved but re-education may teach the hypertensive more satisfactory means of adjustment.[25] The physician who allows the patient to talk about himself and his problem, instead of his blood pressure and symptoms, may accomplish a great deal by this catharsis. It is important to reassure the patient and to discuss the disease with him. Very often we have found that the fear aroused by high blood pressure is more incapacitating than the disease. Activity is often a better prescription for such patients than the advice to take it easy, which may suggest invalidism and even death to the patient. It has been suggested that in some patients psychoanalysis may be necessary and effective, but most investigators believe that in hypertensives the aggression and anxiety are close to the surface and can be modified by a less intensive program.

Diet

When the blood pressure is very high, i.e., over 220 systolic or 120 diastolic, or when the hypertension is progressive, regulation of the diet is often successful in lowering it. The cardinal principles of dietary control are restriction of salt and, in overweight persons, a low caloric intake. Although there is no unequivocal proof that obesity causes hypertension, there is no doubt that obesity is more common in people with hypertension, and increases the severity of the disease and its mortality rate. We have found the frequency of obesity in hypertensives to be twice as great as in controls of similar age.[26] A reduction in weight is usually followed by a reduction in blood pressure and by clinical improvement. It is therefore essential to avoid overweight in those who suffer from hypertension.

Although a rice diet is only rarely indicated and is not practical for long-term therapy, Kempner,[27] who introduced it, performed a great service by re-emphasizing the value of a low salt diet in treating hypertension and hypertensive cardiovascular disease. In probably one-third to one-half of the patients the rice diet is at least as effective as any other type of therapy. A strict rice diet may be used for some weeks in an acute exacerbation of hypertension or in its malignant phase; for longer periods, however, a diet containing 0.2 gm. of sodium daily may be effective. In mild cases a diet with 0.5 gm. of sodium is sometimes effective. In some cases ion exchange resins enhance the effect of a low salt diet.

In practice, a low salt diet cannot easily be observed. Not only is sodium present in many foods that would seem to be sodium-free, but it is also found in many laxatives, carminatives, headache remedies and sedatives, in tooth pastes and mouth washes and, in some localities, even in the drinking water. The difficulty in preparing a salt-free diet has diminished as the number of salt-poor prepared foods has increased.

Drugs

Sedatives have long been routinely used in hypertension. The favorites have been chloral, bromides and phenobarbital. They are of some aid in the milder cases, in conjunction with other measures designed to ease stress and strain; in more severe cases, however, they are ineffective.

For a time thiocyanates were used to lower the blood pressure. However, only a small percentage of patients were helped thereby and the results were unpredictable. Occasionally, dangerous or even fatal reactions occurred, even under the best supervision.[28]

In recent years several drugs have been introduced for the purpose of decreasing hypertension. Some have already been discarded but others have shown promise, although it is still too soon to attempt a final evaluation of them. Among the latter are the methonium compounds (C5, 6), *Veratrum viride*, 1-hydrazinophthalazine (C5968), the dihydrogenated ergot alkaloids, dibenzyline (688A) and *Rauvolfia serpentinum*. These drugs act on different parts of the nervous system: 1-hydrazinophthalazine, the dihydrogenated ergot alkaloids and *Veratrum viride* act centrally on the hypothalamus; the methonium compounds block the sympathetic (and parasympathetic) ganglions, and dibenzyline (688A) acts on the peripheral nerve endings (Table 2).

Although all these drugs temporarily lower the blood pressure in many hypertensive patients, and although several are particularly effective when given parenterally in acute hypertensive crises, their value in the continual treatment of essential hypertension is still undetermined. It seems fair to say that thus far the results have been only partially successful and that there are numerous pitfalls in the use of these drugs. On the other hand, from various reports it appears that they occasionally provide a means, hitherto unavailable, of correcting cases of malignant hypertension. It is probable that no one drug alone is effective in a large number of patients. The administration of two or more of the drugs in combination will therefore probably be necessary. This is particularly true of the methonium salts and 1-hydrazinophthalazine; when both are given, the drop in blood pressure is definitely greater than when either is administered alone. Furthermore, various dosages and combinations of oral and parenteral administration have been suggested. There is a greater variation in individual response to these compounds than to many others, and the optimum dosage must be determined for each patient. All these drugs may produce undesirable side effects, which are at times dangerous and even fatal. Their use must therefore be continuously supervised. It is wise to begin with a small dose and increase it as indicated. Since the effect of these drugs on the pressure is only temporary, they must be taken continually.

TABLE 2

DRUGS RECENTLY INTRODUCED AND THEIR MODE OF ACTION

DRUG	MODE OF ACTION
Veratrum viride	Central
1-Hydrazinophthalazine (C5968)	Central
Dihydrogenated ergot alkaloids	Central
Hexamethonium (C6)	Ganglion blockade
Dibenzyline (688A)	Peripheral nerve endings
Thiocyanates	Uncertain
Rauvolfia serpentinum	Uncertain

Our knowledge of these drugs may be summarized as follows:

Methonium compounds—The hexamethonium (C6) compounds have been found to be more effective and safer than the penta (C5) compounds. The C6 compounds studied include the chloride, bromide, iodide and bitartrate. Although hexamethonium bromide was used first, most recent workers have preferred

hexamethonium chloride which is available orally, in 250 or 125 mg. tablets,* and for injection in vials of 10 cc.† The dosage of the tablet is expressed in milligrams of the whole salt whereas the solution contains 100 mg. of the hexamethonium ion per cubic centimeter and dosage is calculated on this basis.

The action of the compounds is to block all the autonomic ganglions.[29-32] They thus shut out the vasoconstrictor impulses and produce a chemical or medical sympathectomy in many patients. The reduction in blood pressure is usually moderate but may be marked enough to be dangerous. For this reason it is wise to begin treatment with the drug in a hospital. In that case the drug may be given intravenously at first. It is customary to test the effect of an injection of 10 mg. on the blood pressure. This may produce orthostatic hypotension with weakness, faintness and dizziness in the erect position. This reaction promptly subsides when the patient lies down. If there is no reaction or if the reaction is mild, the injection is repeated every 8 to 12 hours and the dose is gradually increased. Injections of 100 mg. have been given two or three times a day. If the drug produces severe postural hypotension, the same dose may be repeated under careful supervision with the patient in the recumbent position, because the reaction usually becomes milder as the injection is repeated. Otherwise the drug may have to be discontinued or small doses given. A wise precaution is to take the blood pressure before giving an injection since the dosage probably should not be given if the blood pressure falls to 150 mm. systolic. If there are symptoms of postural hypotension, they may be alleviated by wearing an abdominal belt or ACE® bandages.

Although postural hypotension is the most serious reaction to hexamethonium, it may produce other side effects which may prove annoying or even dangerous. Constipation is common and may develop into obstruction or, rarely, paralytic ileus. Urinary retention also may occur. These symptoms may be relieved by 5 mg. of URECHOLINE® sublingually. One of our patients was forced to discontinue the drug on two occasions because of pain in the region of the kidneys. Other side reactions of hexamethonium are usually mild and include blurred vision, drowsiness, palpitation, anorexia and dryness of the mouth.

The oral administration of hexamethonium often produces a satisfactory drop in blood pressure and requires the same caution. If there is a tendency to postural hypotension, the patient should remain near his bed and wear ace bandages. The usual initial dose is 125 mg. four times a day; under observation, this may be gradually increased every two or three days, if necessary, until 2.5 to 3.0 mm. is taken. Higher doses have been administered in some cases without untoward effects, e.g., one of our patients has taken 4 gm. daily for six months. A smaller dose is required in patients on a low salt diet and in those who have had a sympathectomy.

1-Hydrazinophthalazine—1-Hydrazinophthalazine, first known as C5968, is now available in 10, 25 and 50 mg. oral tablets, and in ampules containing 20 mg. per cubic centimeter.‡ Its action is exerted at several levels but, it is believed, principally on the hypothalamus. It probably reduces the flow of sympathetic vasoconstrictor impulses from this center. It is the only drug which lowers blood pressure while increasing renal blood flow.[33] The daily dosage varies widely—from 75 to 900 mg. A dose of 200 mg. four times a day is frequently necessary. The drug is relatively nontoxic and rarely causes significant postural hypotension. It may, at first, produce headache, stuffy nose, tearing, tachycardia, nausea, vomiting, tremor and cramps but they may be prevented or alleviated by giving an antihistaminic and sedative. These side effects usually subside in one or two weeks. The drug is most effective in hypertension which has persisted following sympathectomy, and it has also been used in the toxemia of pregnancy.

Most workers have found a combination of hexamethonium and 1-hydrazinophthalazine

*Trade names: Methium, Esomid.

†Trade name: Bistrium Chloride.

‡Trade name: Apresoline.

more effective in reducing blood pressure than either drug alone.[30-32] The combination has been found valuable even in some cases of malignant hypertension without nitrogen retention but it is not without danger and is still in the experimental stage. The effect of each drug should be determined before both are given simultaneously. Treatment is therefore best started in a hospital. Several schedules of dosage have been suggested. Freis and his co-workers[30] achieved their best results with a combination of hexamethonium subcutaneously and 1-hydrazinophthalazine orally, as follows: 10 to 75 mg. of hexamethonium were injected every 12 hours, and 50 to 150 mg. of 1-hydrazinophthalazine were given six hours after each injection; thus the patient alternated the two drugs every six hours. Such treatment, for a long time, is not suitable outside a hospital. Schroeder[31] gave both drugs orally every four hours but found it necessary to administer them throughout the night. Since sleep alone also lowers the sympathetic tone, one wonders whether it is useful to administer such drugs at night. Schroeder advised initial small doses in order to reduce the blood pressure slowly, and a gradual, slow increase in the dosage. Deaths attributable to the medication have occurred in his series of cases. Extreme caution is required in patients with a history of some cerebrovascular accident. He found that hexamethonium, if given first, usually prevented the side effects of hydrazinophthalazine, and he recommends this order of administering the drugs.

Veratrum viride—Most of the experience has been obtained with alkaloid preparations of *Veratrum viride*.* Its effect is variable and reports indicate a successful response in 20 to 50 per cent of patients treated. The failures are in part attributable to the frequency of resulting nausea, vomiting, excessive salivation, tightening of the chest and paresthesias.[34] In order to lessen these side effects the drug is taken after breakfast and about two hours after lunch and dinner. The initial dose is 1 to 2 mg. three times a day, and this may be increased to 9 to 15 mg. daily if it is tolerated. If its administration is carefully supervised, *Veratrum* is effective in some patients. Circulatory collapse may occur and bradycardia is not uncommon. The hypotension can usually be counteracted by ephedrine (30 to 45 mg.) or NEO-SYNEPHRINE® (5 mg.) by muscle. The bradycardia, which is probably the result of an effect on the carotid sinus, is abolished by atropine (0.5 to 1 mg.), which may relieve some of the other side effects.

Veriloid is far more effective when given intravenously or intramuscularly in hypertensive encephalopathy.[35] The intravenous solution contains 0.4 mg. veriloid per cubic centimeter and the therapeutic dose is 0.15 cc. (0.06 mg.) per 10 pounds. The calculated dose is diluted to 10 cc. and injected very slowly until the blood pressure falls or side effects are noted. These include nausea, dizziness and arrhythmias. The blood pressure is recorded frequently during the injection.

Recently more favorable results have been reported with protoveratrine, a principal derivative of *Veratrum album*.[36] Oral tablets of 200 and 500 mcg. are available. The oral dose suggested is 500 to 1500 mcg., with small reinforcing doses of 250 mcg. at 10:00 A.M. and, probably, after lunch. Given this way, the drug rarely produced nausea and vomiting and usually relieved headache. However, others have not found protoveratrine to be effective when given orally.[37]

Dihydrogenated ergot alkaloids—The dihydrogenated alkaloids of ergotoxine include dihydro-ergocornine, ergocristine and ergocryptine. They produce peripheral vasodilatation and central depression of vasopressor responses. They also cause bradycardia. Their effect on blood pressure has been inconstant but they do increase cerebral circulation and thus may relieve headache, dizziness, tinnitus and visual disturbances, even when the blood pressure is not markedly decreased. At present they are available for injection only.† The initial dose is 1 or 2 cc. (0.3 to 0.6 mg.) intramuscularly. If the response is adequate this dose is administered three times a week; if not, the injection is given daily.[38] Usually

*Available commercially as Veriloid, Veratrite, Verutal, etc.

†Trade name: Hydergin. Each 1 cc. ampule contains 0.3 mg., i.e., 0.1 mg. each of dihydro-ergocornine, ergocristine and ergocryptine.

mild side effects—stuffy nose, flushing and nausea—may occur.

Dibenzyline (688A)—Dibenzyline is not yet available commercially. It is a derivative of DIBENAMINE® and is more effective and less toxic than dibenamine. It blocks the sympathetic impulses at the periphery, i.e., at the neuro-effector junction within the cells. Only a few preliminary reports on the effect of 688A on hypertension, in small series of cases, have appeared. When enteric-coated tablets were used the effect was irregular or slight. However, Moser and his co-workers[39] observed significant lowering of the blood pressure following the administration of gelatin capsules. Orthostatic hypotension, weakness, drowsiness, nasal stuffiness and palpitation proved annoying to several patients but were not serious. The dosage given was 1 to 4 mg. per kilogram of body weight. Further investigation of dibenzyline is necessary.

Rauvolfia serpentinum—*Rauvolfia serpentinum* is obtained from a plant growing in India and other areas of the Far East. It has long been used there in cases of hypertension and good results have been reported.[40] It probably acts on the cerebral centers, and possibly on lower ones as well. It appears to be quite safe. It produces drowsiness, lassitude, diarrhea, anorexia, nausea and vomiting in only a few patients. The dose is 1 tablet three times a day, p.c. *Rauvolfia serpentinum* should be given a trial in this country.

Miscellaneous—Numerous other preparations have been used in treating hypertension but they are still in the experimental stage. They include sodium nitroprusside, RO 2-2222 (a thiophanium compound), sulfhydryl compounds, renal extracts, oxidized marine oils and, in malignant hypertension, water-soluble pyrogens intravenously.

Sympathectomy—Although this operation was introduced two decades ago, there is still much disagreement as to its value and its indications.[41] With occasional exceptions[42] it is generally agreed that no present test enables one to predict which patients will be benefited by the operation. Various clinical criteria are employed. Some recommend the operation early for those who show little visceral involvement. Others have reported good results in advanced cases, particularly in those with malignant hypertension or heart failure. Apparently the ideal candidate for the operation is one who, regardless of age, is well adjusted emotionally and displays little cardiac, renal or cerebral damage, and whose blood pressure shows progressive elevation but tends to fall with rest and medication.[41]

Although the majority of physicians appear indifferent to sympathectomy, it has a number of ardent proponents. Every physician has probably observed one or more impressive postoperative results. Smithwick[43] found a significant reduction in blood pressure for five years or more in half his cases. Ray[44] found that the blood pressure returned to normal, or approached normal, in 28 per cent and that it dropped significantly in 31 per cent; i.e., a good result was obtained in practically 60 per cent of the cases. Their available data suggest that the reduction in the blood pressure lengthens the survival time. However, others have reported good results in only a small percentage of cases. The operation is a major one and convalescence may be prolonged. It is essential to remove a large portion of the thoracic and lumbar sympathetic chain. Postoperative neuralgia and postural hypotension may be severe for some time thereafter.[45]

Total and subtotal adrenalectomy, sometimes combined with sympathectomy, have recently been performed in patients with severe hypertension and congestive failure but these procedures are still experimental.[46]

It is questionable whether any method of therapy can now cure essential hypertension or whether lowering the blood pressure lengthens the period of survival of these patients. While some postsympathectomy reports seem to be promising, more definite data are necessary in large series of cases and after various types of medical treatment before the operation is undertaken.

References cited are included in the authors' reprints and are available on request to the Editorial Department of *Postgraduate Medicine*.

Pediatrics IN GENERAL PRACTICE

Surgical Treatment of Infantile Hydrocephalus and Meningocele

For general practitioners, who handle more than 85 per cent of all pediatric care, POSTGRADUATE MEDICINE *here presents authoritative, up-to-date summaries by specialists in pediatric problems.*

TRACY J. PUTNAM

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Historical Introduction

TRACY J. PUTNAM

THE condition of infantile hydrocephalus is unmistakably portrayed in ancient Greek votive statuettes, but the first written description of it which I have been able to find is that of Celsus.[1] He describes a disorder of infants "where the fluid distends the skin, causes a swelling of it, and yields to the pressure of the finger: This the Greeks call *hydrocephalus.*"

This early description calls attention at once to the fundamental characteristic of infantile hydrocephalus, namely, the increase of intracranial pressure. The remaining clinical details were gradually filled in during the nineteenth century: the essential facts that hydrocephalus is a common disorder, occasionally present at birth, but is more apt to come on during the first year of life; that it is often associated with spina bifida, and may be precipitated by repair of a meningocele, and that children afflicted with hydrocephalus do sometimes survive to adult life, occasionally with preserved intelligence. Unfortunately, a serious error was introduced by the pathologic anatomists of this period, namely, the confusion between the condition of increased intraventricular pressure or true hydrocephalus according to Celsus, and the enlargement of the cerebral ventricles resulting from atrophy, formerly called "hydrocephalus ex vacuo."

The distinction between spontaneous infantile hydrocephalus and tuberculous meningitis became clear with the introduction of lumbar puncture. A recognition of the physiology of the condition resulted from the work of Dandy and Blackfan in 1918, and this laid the foundation for a sound surgical approach. The condition of subdural hygroma gradually became familiar to pediatricians during the 2 following decades, and its surgical treatment became established. Cases of hydrocephalus resulting from obstruction of the aqueduct by tumors, atresia or inflammatory diseases (such as toxoplasmosis) have been recorded from time to time.

This article deals solely with the treatment

of spontaneous communicating infantile hydrocephalus, with or without meningocele. Medical treatment of these conditions appears now to be abandoned, and spontaneous recovery is so rare that it has eluded statistical evaluation. A variety of surgical procedures is now available for the relief of infantile hydrocephalus, however, of which one type, to be described in detail, has been well standardized for 18 years. It can now be performed with negligible mortality and with a high proportion of excellent results in well selected cases.

FIGURE 1. Daniel S., born July 1934. Photographs taken just before coagulation of choroid plexuses in September 1934, in 1940 and in 1952, at time of graduation from high school.[13 (Case 8)]

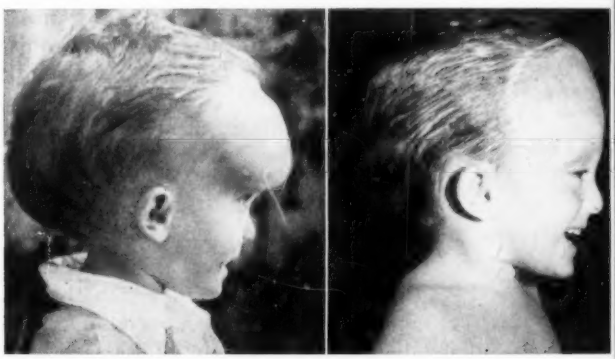

FIGURE 2. Sandy G., age 3 years in November 1949, just before endoscopic coagulation of the choroid plexuses, and in May 1952, after reduction of intracranial pressure had permitted plastic repair of elevated flap of transfrontal operation performed elsewhere. Intracranial pressure continues normal; excellent intelligence.

FIGURE 3. Diane C., age 5 months in November 1950, just before coagulation of choroid plexuses, and in March 1952. Intracranial pressure now normal.

Destruction of the Choroid Plexuses

The conception that the spinal fluid is secreted by the choroid plexus originated with Magendie. Isolated, and on the whole unsuccessful, attempts to relieve hydrocephalus by destruction of the plexus were carried out in the early years of this century. The possibilities of surgical treatment were, however, first systematically explored by Dandy between 1918 and 1922.[2,3] He showed experimentally that removal of the plexus caused collapse of a blocked lateral ventricle in animals, and described a technic for removal of the plexus under direct observation in cases of nonobstructive hydrocephalus (1918).[2] He never presented statistical studies of his cases, however. In 1932[4] he stated that "the survival period has not been long enough to be certain of cures," and in 1938,[5] "I have had several undoubted cures, resulting from this method."

My own technic was published in 1934.[6-9] It is based on the use of a distinctive type of coagulating endoscope, utilizing a rod of optical glass as a viewing system and also as a carrier for two electrodes and a lamp. This has the following advantages: (1) It pro-

vides an extremely wide optical aperture which permits visualization of the ventricular contents even when the fluid is bloody. (2) No current passes through the brain. There is a small intense electrical field between the electrodes. (3) The diameter of the instrument may be kept sufficiently small to permit introducing it into the frontal and temporal horns even before the ventricles have become greatly dilated. This instrument was developed after unsuccessful trial of conventional endoscopes bearing unipolar coagulating electrodes. The employment of these tended to produce necrosis of the floor of the ventricle, and the operative field was poorly seen. An endoscope of the conventional type, with provision for irrigation, was devised by Scarff in 1936,[10] and he still uses it, reporting excellent results.[11,12] In his last series of 19 cases, there was only 1 "operative" death, and the result was excellent in 15 cases. Other surgeons have reverted to Dandy's method, but no significant statistics have been reported.

Results

My results were last fully reported in 1943.[13] Disregarding other conditions, 71 operations were reported in 42 cases, with 11 operative deaths, of which 7 occurred in the first 17 cases. Since then, 20 operations of this type have been performed, in 10 cases, with no operative deaths.

I have been unable to follow 3 of these patients who were operated on in New York between 1943 and 1946, but all were doing well in 1946. Of the 7 patients operated on since 1947, 4 are still alive and doing well, with maintenance or improvement of mentality. One patient was incompletely relieved by cauterization of the choroid plexuses, or by an additional ventriculomastoidotomy, but has done well since a tube was inserted from the subarachnoid space into the peritoneal cavity. One was apparently relieved of hydrocephalus but died of unrelated causes. One died following an attempt at a third ventriculostomy.

The mentality has improved following relief of pressure in all cases. When the operation was performed before deterioration began, the results were uniformly excellent.

Since many detailed case reports have been presented by Scarff[10-12] and in my previous publications,[6-9,13] I shall content myself with a few general observations on the indications for operation, details of technic and results.

First, this operation is a safe one—safer perhaps than ventriculography in such cases, and apparently safer than the recently proposed drainage operations. It is probably safer to operate than to wait in the early stages of the disease in the hopes that it will become arrested spontaneously.

Second, the outlook is excellent if patients are referred for surgery before the mentality is affected and before there is irreparable damage to the brain. Ideally, the decision for operation should be made in cases in which the presenting symptom is a swelling of the fontanelles, and the diagnosis of infantile hydrocephalus is made on the basis of a ventricular puncture under sedation. The decision to operate should be mandatory if these manifestations follow repair of a meningocele. As I have pointed out, this procedure serves to rule out meningitis, toxoplasmosis and subdural hygroma, and usually renders ventriculography unnecessary.

Third, prognosis depends chiefly on the patient's intellectual endowment at the time of operation, but the degree of enlargement of the head and thinning of the cortex are limiting factors. Sometimes patients whose ventricles are enormously dilated may show an unexpected degree of intelligence, and Scarff[11] has shown that the ventricular wall may grow thicker following relief of intracranial pressure. Gross enlargement of the head may ultimately produce secondary adhesions about the base, in which case destruction of the plexuses may not completely relieve the pressure. Many of the poor results, both in my series and in Scarff's, would undoubtedly have been avoided had the patients come to operation sooner.

Fourth, operation may be considered justified even in cases of mediocre mentality, and when the head is grossly enlarged. Such individuals do not necessarily die; they some-

times grow up to adult life with monstrous heads and progressively impaired mentality. It may seem wiser to attempt to arrest the growth and preserve the remaining mentality, even at an advanced stage. Despite relief of pressure, patients with poor mentality appear to have a poor life expectancy.

Fifth, ventriculostomies of various types may prove helpful as an adjuvant to cauterization of the plexus, which appears to be the operation of first choice in cases of communicating hydrocephalus. Certainly the drainage operations are more likely to succeed and less likely to lead to complications if the production of fluid is restricted.

Sixth, certain technical refinements have been added to the technic I published in 1943.[13] Suture of the pia to the dura minimizes the danger of collapse of the ventricle at operation or the formation of subdural cysts. Drainage of the ventricle through a tiny plastic tube diminishes the postoperative reaction and in one case made it possible to operate on both sides at one sitting.

Seventh, no case should be abandoned after cauterization of both sides without a reinspection to make quite certain that no tags of plexus were left behind. This is particularly important if the preliminary operations were performed with the cystoscope type of ventriculoscope.

Eighth, coagulation of the plexuses may be of great help in treatment of other conditions which involve an increase of intracranial pressure, for example, postmeningitic hydrocephalus, and large, tense, sessile meningoceles which do not destroy the function of the sphincters.

Drainage Operations for Relief of Communicating Hydrocephalus

Little has been added to this subject since the scholarly review of Davidoff[14] in 1929. The outlook for the success of various types of operations by which fluid is drained into some body cavity has been greatly improved by the introduction of fine polyethylene tubing for the purpose.[15] A few successful case reports of drainage into the ureter[16,17] and antrum[18] have appeared in the literature. Still rarer are operations on the Arnold-Chiari malformation.[19]

A brief report by Walker,[20] which perhaps will be published in amplified form by the time this review appears, summarizes the situation. He says: "On the basis of the medical literature and the records of the Johns Hopkins Hospital, the results at the end of 2 years were as shown in the tabulation below."

It is not clear whether "plexotomy" includes endoscopic coagulation, or whether it refers to Dandy's operation of removal of the plexus. In either case, a comparison between this table and the results reported in the present article speaks for itself.

Conclusion

Infantile hydrocephalus is a common condition, perhaps as common as harelip or clubfoot. The condition is easy to recognize, even in early stages. There is a well established surgical operation which carries a small mortality and an excellent prospect of relief in early cases. To my mind, it is as gross malpractice to permit one of the unfortunate children with promising mentality to slip past

OPERATION	NO. OF CASES	OPERATIVE MORTALITY	RESULTS AFTER TWO YEARS*	
			Alive	*Dead*
Plexotomy	194	70	31	105
Third ventriculostomy	197	44	39	81
Arachnoidoperitoneostomy**	105	12	41	6
Arachnoidoureterostomy	86	6	17	28
Ventriculocisternostomy	25	8	9	9

*Only the patients whose states were definitely known two years after operation coded.

**Based largely on the series of Arendt, whose results are not well documented.

the period of election without a trial of operation, as it is to permit a patient with meningitis to go without antibiotic drugs.

Surgical Treatment of Meningocele

Meningocele, spina bifida and similar defects occur in almost endless variety. In many cases, the sac is pedunculated, with no signs of increased intracranial pressure and no paralyses. Under such circumstances, simple plastic repair of the sac, wherever situated, gives excellent results with negligible mortality.[21] If repair of such a defect precipitates a hydrocephalus, cauterization of the choroid plexuses can be counted on to relieve it.

Sometimes the intracranial pressure is obviously elevated before operation on the sac is undertaken, and sometimes plastic repair of the sac appears difficult or dangerous because of leakage or because the sac has a wide base or is covered by a membranous integument. Under such circumstances, coagulation of the choroid plexuses should be carried out as a first step.[7, 13, 22] This will usually bring the defect within reasonably easy reach of surgical repair. Illustrations of the effect of relief of pressure are given in the references cited and a fresh report is now being prepared.

The question of operation on meningoceles of any type becomes much more difficult if paralyses are present. In general, the presence of paralysis of one leg alone may not be a contraindication for operation, but complete paralysis of the sphincters is usually incompatible with tolerable existence. Sometimes there is an improvement of function following operation on a meningocele, but it is the exception. Children with paralyzed sphincters sometimes survive to adult life with or without operation. If the sac is painful, this may constitute an indication for operation.

Technical Details

Meningoceles located in the lumbar region are often best approached through a transverse incision, to keep as far as possible from the rectum. The dissection of pedunculated sacs is simple. Sessile defects should be carefully dissected away from the spinal muscles, down to the communication with the spinal canal. The dissection of the spinal nerves, if they are caught in the structure, should begin at the upper end, as they are usually more clearly seen there. Special attempts to preserve the area vasculosa, formerly recommended, seem to have been generally abandoned. There is usually a small neck, over which the dura or paraspinal fascia may be closed, then the erector spinae muscles sutured over the midline. The use of subcuticular suture, dressings sealed to the skin and antibiotics is advisable.

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Sudden and Unexpected Death in Infancy

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SUDDEN death occurs during the course of many diseases, but most distressing to family and physician is the unexpected sudden death of an apparently normal infant. The parents are usually beset with fears of possible errors of omission or commission, and it behooves the physician to make every attempt to ease their sorrow and feelings of guilt by a thorough and painstaking evaluation of the cause of death.

Many vague terms have been used on death certificates without providing a plausible explanation of death. Such terms as status thymicolymphaticus, accidental mechanical suffocation, asphyxia and anaphylaxis have often been used, leading to deeply rooted misconceptions, misinterpretations and superstitions.

During the past 15 years clarification of the problem has been made possible through skillful examination of pathologic tissue by interested physicians who are unwilling to take anything for granted. The majority of the unexplained cases can be labeled with a definite cause of death after proper examination is made.

Sudden death during the course of a known disease is not difficult to explain; the real problem lies in finding the causes of completely unexpected sudden deaths of infants and small children.

Suffocation

The Metropolitan Life Insurance Company in 1942 considered mechanical suffocation the greatest hazard in infancy. Many investigators were disturbed by several factors at that time. One of the most striking was the high frequency of suffocation coincidental with the high incidence of upper respiratory infections during the fall and winter months. It was also apparent that the greatest number of deaths attributed to so-called suffocations were of 3 to 4 month old infants rather than of helpless newborn infants. Accumulated evidence justified the conclusions that mechanical suffocation caused by extrinsic agents was unusual. When it does occur, the infant is usually debilitated or premature. Garrottment by defective sleeping apparel, lodgment of an infant between bars of a defective crib, and overlying of the infant by an adult can cause suffocation of a healthy infant.

Wooley[1] failed to alter substantially the oxygen and carbon dioxide concentration under bedclothes, pillows and mattresses which he used to simulate conditions that might cause suffocation. Davidson, reporting on 318 cases of infants whose deaths were attributed to suffocation, found this diagnosis to be correct in only 25 cases.[2] Of these 25, 18 infants

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died of mechanical suffocation while sleeping in bed with another person. Werne and Garrow[3] clarified many cases in which the deaths allegedly were due to suffocation.

Despite circumstantial evidence, a physician is justified in rejecting this diagnostic possibility until microscopic studies have eliminated all other causes of death. The self incrimination of remorseful parents in a suggested case of suffocation should be sufficient stimulation for a painstaking autopsy.

Thymic Causes

The deeply rooted misconception of thymic deaths (mores thymica) has an ancient origin. Carr[4] in 1945 initiated new controversy supporting the idea of thymic relation to sudden death. He proposed that abnormality of the thymus could be related to unexpected death, the mechanism being of secondary importance. Many authorities before and since have refused to accept a condition such as status thymicolymphaticus or lymphatic constitution. They believed that significant causes of death can be ferreted out if detailed studies are done.

Probably the confusion concerning the pathologic potential of the thymus arises from a lack of knowledge of its normal function. At various times the thymus has been thought to have a connection with somatic growth, parathyroid function, adrenal function, calcium metabolism, gonadal development, osseous development, general nutrition and epiphysial closure. Abnormal thymic enlargement has been reported repeatedly in myasthenia gravis, rickets, adrenal hypoplasia, Addison's disease, acromegaly and exophthalmic goiter.

In the light of our present day knowledge several general points concerning the thymus can be made.

1. The gland varies in size more than any other organ. Boyd[5] showed the gland to be smaller than accepted pathologic standards in infants and children who had died accidental deaths. Farber[6] in a long series of consecutive autopsies concluded that the gland was not diseased in any case although large glands occurred without abnormal symptoms. He found significant causes of death other than the thymus in all the latter cases.

2. The thymus is largest during periods of rapid growth, with involution at puberty and an increase in size with old age.

3. A decrease in size of the gland seems to occur in cases of malnutrition.

4. Position of the gland in the anterior mediastinum is as important as its size and weight. Caffey[7] pointed out that the broad mediastinal shadow in infants indicates a thin, superficially placed gland which has not been compressed and molded posteriorly between fully expanded lungs. The supracardiac shadow becomes widened during inspiration so that the size of the thymic shadow on the roentgenogram cannot be interpreted accurately even when full inspiratory anteroposterior views and oblique and lateral views are taken, nor can one demonstrate possible encroachment of the gland upon the trachea. It is hard to accept Carr's belief that the thymus, a contiguous structure to the heart which compresses with each breath, can disrupt the heart or interfere with the recurrent laryngeal or vagus nerves.

Although it is probable that roentgen radiation will shrink a thymus gland and that the amount of radiation used is not harmful, it seems most improbable that the gland is a cause of obstruction to its surrounding structures. It also seems highly improbable that abnormality of the thymus gland is primarily implicated in sudden, unexpected deaths in infants.

Aspiration of Fluids

The important mechanisms of death (Table 1) have been clarified at autopsies in deaths incorrectly attributed to suffocation and to thymic causes, as well as in sudden unexplained deaths. Aspiration of formula, vomitus, excessive secretions, foreign bodies or amniotic fluid is not uncommon as a cause of sudden death. In this light it is important to consider the advisability of a face-down position for sleeping infants. Physiologically the face-down position allows for dependent drainage of secretions from the tracheobronchial tree into the oropharynx. The face-down position is of exaggerated importance as the

TABLE 1

MECHANISMS OF UNEXPECTED SUDDEN DEATH

1. Aspiration
2. Infection
   a. Pulmonary
   b. Generalized sepsis
3. Hemorrhagic
   a. Intracranial
   b. Intra-abdominal
   c. Adrenal
4. Congenital anomalies
5. Anesthesia
6. Miscellaneous

cause of mechanical suffocation. The alternative supine position is associated with increased danger of aspirating secretions or other materials which may be pooled in the posterior pharynx.

Infection

Excluding aspiration, the most important cause of sudden death is infection. In pulmonary infection definite physical signs either are notoriously absent or are not evident to an unpracticed eye. Moritz[8] has pointed out that in the young and old the course of pneumonia is very rapid, frequently not longer than a few hours. Adams[9] has considered pneumonia as the primary cause of sudden death in infants. Labate[10] found almost 40 per cent of the deaths due to pulmonary lesions. Although pneumonitis is more common, one can consider aspiration pneumonia in the category of pulmonary infection.

Pneumothorax, associated with pulmonary disease or occurring in its absence, is fairly frequent in infancy and as an added insult can cause death. Emphysematous blebs occur with bronchopneumonia and these rupture causing a direct connection with the pleural cavity. Spontaneous pneumothorax, without infection, occurs in association with trauma to the chest cage or accidentally following a tracheotomy.

Generalized sepsis is often present without antecedent symptoms or signs. It may or may not be associated with clinical meningitis. The importance of fulminating infection in sudden deaths in infancy has been stressed. The *Streptococcus* is the most common organism but other bacteria or viruses are frequently the etiologic agent. Death from Eastern equine encephalitis, for example, can occur in 24 hours or less. In rapidly fatal sepsis, bacteremia may be so rapid that no impressive localization in any one particular organ can be found at autopsy.

Hemorrhage

Hemorrhage can be classified as the next cause of sudden death, with intracranial hemorrhage being the most common type. This can occur as a complication of the passage of the fetal head through the birth canal with a tentorial or falx tear, or with rupture of a cortical or larger vein. Subarachnoid hemorrhage will occur with cortical vein rupture.

Infants with intracranial hemorrhage are often well for a period of time after delivery, when the symptoms occur with great suddenness. One must also remember that intracranial hemorrhage often occurs after cesarean section or after vaginal delivery without apparent trauma as well as following difficult births. Intra-abdominal hemorrhage with sudden rupture of an encapsulated hematoma of the liver sometimes occurs. The latter usually has its origin at delivery due to ill advised handling or vigorous resuscitative attempts. Adrenocortical damage and hemorrhage, associated with generalized sepsis, are commonly observed. This hemorrhage can be either microscopic—for example, associated with pulmonary infection, the combination of which causes sudden death—or massive and bilateral with clinical evidence of sudden circulatory collapse, as in the Waterhouse-Friderichsen syndrome.

Congenital Anomalies

In autopsy records of hospitals, congenital anomalies of the heart, great blood vessels, lungs, digestive tract and brain rank high as causes of sudden death in infancy. Many of these lesions can be compatible with life beyond infancy, but unexpected death in the neonatal period may occur as the result of a complication of a congenital cardiac anomaly.

Anesthesia

Another category which we should consider is that of the disturbing deaths following or attendant to anesthesia. Whether or not there may be a sensitivity to the anesthetic agent, to atropine or to other drugs given preoperatively, or whether aspiration occurs while the infant is under anesthesia, a considerable number of these cases show evidence at autopsy of mild infection or overwhelming sepsis which in no way differs from the situation mentioned earlier in this discussion. Aspiration of foreign material or blood by an anesthetized patient is no longer as great a danger with the new diagnostic technics, proper postural drainage and bronchoscopy.

Miscellaneous

All the causes of sudden death cannot be considered in this short discussion and many minor causes of death can be mentioned in passing. Poisonings can occur but are rare, as are hypoglycemia and anaphylactoid deaths in eczematoid infants. Other diseases such as laryngotracheal bronchitis have a predictable possibility of causing sudden death.

In conclusion it is well to emphasize once again the extreme importance of complete and detailed autopsy in every case of sudden and unexpected death in infancy, in order to arrive at a satisfactory diagnosis.

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Postgraduate Clinical NOTES

11. RESUSCITATION OF THE NEWBORN

1. The principles of adequate resuscitation in the severely asphyxiated newborn infant include direct exposure of the larynx, thorough suctioning of both the pharynx and tracheobronchial tree, insertion of an endotracheal tube, and manual control of respiration with 100 per cent oxygen supplied by positive pressure apparatus.

2. The use of complicated mechanical devices and analeptic drugs is questionable.

3. Time lost in beginning effective infant resuscitation may never be regained.

Ellis N. Cohen, Resuscitation of the newborn, *Minnesota Medicine*, August 1952, page 750.

The Treatment of Pinworm Infection in Children

THOMAS S. BUMBALO AND FRANCIS J. GUSTINA

E. J. Meyer Memorial Hospital and University of Buffalo School of Medicine, Buffalo, New York

Stool Examination Seldom Reveals Evidence of Pinworms! Obtaining Diagnostic Specimen is a Simple Office Procedure

Incidence

209 Million Cases in the World Indicate That Pinworms Are the Most Common and Widely Distributed of Human Helminth Parasites

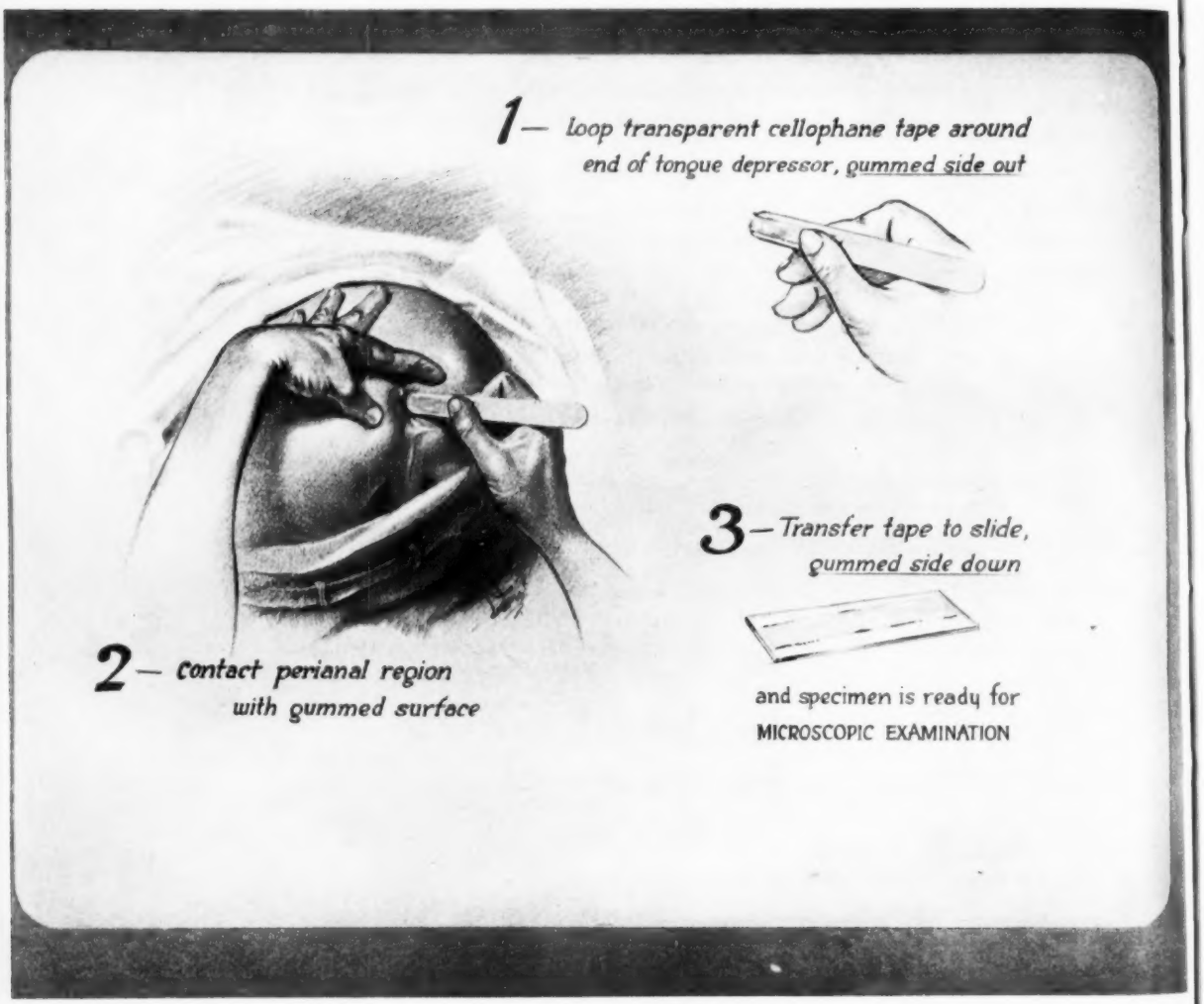
18 Million Cases in the United States and Canada!

	Per Cent
UNITED STATES	
White persons less than 20 years of age	40
Negroes less than 20 years of age	10
WASHINGTON, D.C.	
Preschool children	35
School children	51
Adults	22
Boston, Massachusetts	
Children	38
San Francisco, California	
Children	63
Buffalo, New York*	
Children	17
CANADA	
Toronto, Ontario	
Children	60
PHILIPPINE ISLANDS	
Manila	
Children	75
MEXICO	
Mexico City	
Children	95
PANAMA	
Children	95
HOLLAND	
Amsterdam	100
RUSSIA	17

*E. J. Meyer Memorial Hospital, 1,106 inpatients and outpatients.

Diagnosis

The diagnosis of pinworm infection is a simple office procedure. The method used in this study was a modification of the Graham SCOTCH® tape swab technic. A piece of ordinary scotch tape ½ inch wide and about 3 inches long was looped over the end of a tongue depressor with the adhesive surface on the outside. The ends of the scotch tape were held firmly against the tongue depressor with the thumb and index finger. The adhesive surface of the scotch tape was then touched to the anal orifice, making sure that both sides of the perianal surfaces were contacted by the tape. Then the adhesive surface of the scotch tape was firmly pressed, lengthwise, on an ordinary microscope slide and without preparation the slide was examined under the 16 mm. objective. With this technic the microscopic eggs, which are ovoid and asymmetric and which measure 55 by 26 microns and contain the coiled-up embryo, can be readily visualized.


1— Loop transparent cellophane tape around end of tongue depressor, gummed side out
2— Contact perianal region with gummed surface
3— Transfer tape to slide, gummed side down
and specimen is ready for MICROSCOPIC EXAMINATION

DIAGNOSTIC PROCEDURE

MALE *Enterobius vermicularis* (right).

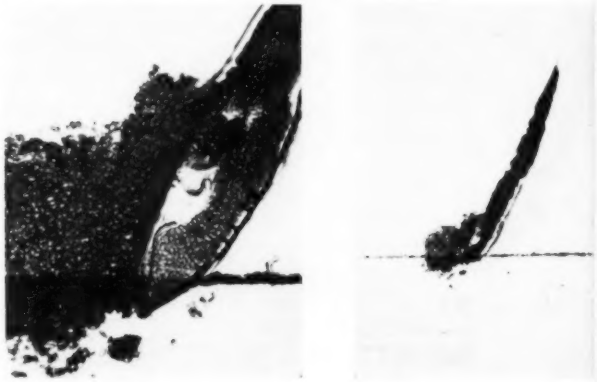
FEMALE *Enterobius vermicularis* (below) under medium low power. Ova are seen within the worm's body. (x 34.)

Life Cycle

The microscopic egg, 55 by 26 microns in size, is swallowed by the human host. Intestinal juices stimulate hatching into young male and female oxyurids, which grow rapidly to sexual maturity. After mating in the lower small intestine and cecum, the male dies and disintegrates. The fertilized female reaches the colon and emerges from the anus after the host has gone to bed. Cooler temperature outside the anus causes violent contraction of the female until it bursts and oviposits 10,000 to 15,000 fertilized eggs in the perianal folds. Scratching fingers transfer fertilized eggs to mouth and the life cycle starts again. (Complete life cycle varies from 14 days to two months.)

OVA *of Enterobius vermicularis* (below) (x 800).

OVIPOSITION (below). Routine examination produced this remarkable specimen—a burst female with expelled eggs.



Symptoms

May be completely absent
Pruritus ani, especially at night
Pruritus vulvae; vaginal discharge
Disturbed sleep
Congestion of anal region
Excoriation of perianal area
Secondary bacterial infection of perianal area
Disturbed behavior attitudes
  Restlessness
  Inattention and lack of cooperation in school
  Feeling of shame and inferiority (due to ridicule when scratching)

Treatment

Drugs

Egressin (0.87 gm. per pound of body weight daily for five days) is an experimental drug and is not available for general use.

Gentian violet (enseals), 1 mg. per pound of body weight divided into three daily doses and given one hour before meals for eight days; course is repeated for eight days after a rest period of one week.

Diphenan: up to 5 years of age, ½ wafer three times a day; 5 to 12 years of age, 1½ wafers three times a day; 12 years of age and older, 2 wafers three times a day. All patients were treated for eight consecutive days.

Terramycin (base and hydrochloride), 10 mg. per pound of body weight divided into three daily doses and given after meals for seven consecutive days.

Strict Personal and Environmental Hygiene

Keep nails cut short
Scrub hands and nails after toilet and before meals
Clean personal linen and bedding
Separate wash cloth and towels for face and body
Sterilize nonwashable toys
Raise room temperature (warm air destroys eggs)
Clean bedroom daily with vacuum cleaner

Follow-Up Smears

Seven days after cessation of treatment all patients were checked by daily scotch tape swab smears to determine the result of treatment. Only those patients who had seven consecutive negative smears were declared cured.

Clinical Results

	NUMBER OF CASES	CURES *Per Cent*	FAILURES *Per Cent*
Egressin	39	54	46
Diphenan	40	30	70
Gentian violet	38	84	16
Terramycin	39	85	15

ACKNOWLEDGEMENT: The authors express their appreciation to Miss Rose E. Oleksiak, B.A. (technician), Mr. Diedrick (medical illustrator) and Mr. L. Bowerman (photographer) for their assistance in preparing this exhibit.

Editorials

Postgraduate Medicine

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CHROMAPHOBE AND CHROMAPHIL

O. H. PERRY PEPPER

WORDS in themselves may start lines of thought and lead one far afield. Let us see where the words of this title take us.

It is just about one hundred years since tinctorial staining of cells was first carried out by Joseph von Gerlach (1820-1896) of Mainz. He employed carmine obtained from the cochineal or the dried female insect as a nuclear stain and also worked with aniline and gold chloride. From this beginning have come, during the past century, all the many stains and methods of staining which have proved so valuable in cytology, histology and pathology. Without these methods medical progress of the past century would certainly not have made all its dramatic advances. Fortunate it is that cells and tissues can thus be colored for microscopic study and can be differentiated by their affinity for various staining agents.

As one would anticipate, the early stains were few and simple; but even with these it must have early been observed that one type of cell behaved differently from another and that some took stains more deeply than others. This phenomenon is now familiar and words have been coined to designate such cells. A chromaphil (Gr. *chroma* = color, and *philein* = to love) is a cell staining deeply. The opposite behavior is indicated by chromaphobe (Gr. *phobos* = fear). These words are in use in histology and pathology. For example, in the anterior lobe of the pituitary there are both chromaphil and chromaphobe cells; basophilic chromaphobe cells are present in the adenomas of this structure. It is very probable that these two types of cell differ not only in their reaction to stains but also in function; but we cannot as yet go very far in drawing any relationship between staining and function. Both types may well be the source of some or all of the many hormones formed in the pituitary. Staining is a fundamental property of the cell, but we know little of its functional significance.

Indeed, color itself in general is still an open field for investigation and argument. It is not known whether color exists of itself or is only in the eye of the beholder. How much, if any, red does a bull see? Color is so universal for all humans except the unfortunate few, that we take it for granted. The truly color-blind are not numerous, but there are

many of us who seem either to register color poorly or to fail to appreciate it fully. Others however are highly color conscious; they love color as much or more than form. Perhaps the words chromaphobe and chromaphil may be transferred from cells to these two types of human individuals. Do these two groups differ in their visual perception of color or is their difference an expression of some fundamental variation in character, personality or training?

The current epidemic of amateur painting which is raging offers us an opportunity for study of this problem in those individuals unspoiled by lessons or technical experience. Many doctors are taking to painting as a hobby, either to take their minds off the worrying duties of their profession or to fill the tedium of inactivity for those who have retired. To all of these, be they 'phobes or 'phils, this problem should be of special interest for they can recognize its psychologic implication in themselves and others.

Let us examine the two types more carefully. A chromaphobe of course uses little paint—he seems to be afraid of it and the paint he chooses is light in color or, as some painters would say, it is high in *value* because it approaches white. He seems to fear color and typically he tends to paint a small picture often failing to reach the edges of the canvas. His technic is meticulous and detailed.

The chromaphil is the opposite—much paint and distinct, often primary, colors. He is expansive and applies the pigment with bold strokes of the brush on a canvas which never seems large enough. Examples of each of these types will come to everyone's mind at once and they can be recognized in every art exhibit.

It is apparent that these two types of individuals are so different that they must vary in fundamentals other than this matter of color. They suggest at once the introvert and the extrovert—but they are not identical with these two groups. All introverts are not chromaphobes, nor all chromaphils extroverts. For instance some introverts find an outlet in chromaphilic painting. Whatever it is we are dealing with, it is something basic in human makeup. Of course it appears in degrees so that we can recognize hyper- and hypo-'phobes and 'phils.

The third dimension of color also finds an analogy in humans. The third dimension is termed Chroma and is to be distinguished from *hue* and *value*. Chroma measures for some colorists the degree to which a color has been altered to approach gray. This is done in order to suggest distance with grayed colors while pigments with higher Chroma would be used for the foreground. Again we find individuals with high and with low Chroma—the latter being those who take a dim or distant view of things and of life in general.

There may be more to all of this than one might conclude from these comments. The reaction of an individual to color may give the most enlightening information about him. It may be that it would be well to discard most of the tests used today by psychologists and others for their various purposes. Intelligence quotients, aptitude tests, Rorschach ink blots and others should perhaps be replaced by the Color Test—are you a 'phobe or a 'phil; what is your Chroma?

How much simpler to hand each candidate for an Army commission or admission to a medical school a child's paintbox, brush and paper. Tell him to paint. His whole mind and psyche will be revealed! Once this method has proved its value, its use will quickly spread to other fields. It will be adopted as better than any of the criteria used so ineffectively today in human eugenics. Two chromaphobes must not be allowed to marry for fear their 'phobic chromosomes might so mingle as to produce nothing but little hyperchromaphobes.

Psychologists are familiar with and interested in many phases of the color problem, especially in children, but they have failed to realize the fundamental fact that all of us are chromaphobes or chromaphils and all that this implies.

Much of this of course is nonsense although, as is often true, there may be some little meaning hidden away in it. At any rate, to some of us words have color and music and it is fun to play with them as in this editorial.

O. H. PERRY PEPPER

SOME MEDICAL PROBLEMS AND TRENDS

FUNDAMENTAL to every medical problem are medical education and the supply of physicians. For every interested group there is a different answer. This is a world-wide problem. Perhaps most significant in finding an answer will be the First International Congress on Medical Education to be held in London, August 21 to 28, 1953, under the auspices of the World Medical Association with the cooperation of WHO and UNESCO.

The problems of the medical schools seem well-nigh insurmountable. The question of financing is being attacked with firecrackers and needs an atom bomb. The Truman committee urged federal funds but the A.M.A. and Eisenhower say "No!" The Association of American Medical Colleges is in between. The answer seems to lie in formulating principles and legislation which would help the situation without putting government in control of medical education. Most of the state universities, such as Illinois, Indiana, Michigan, Minnesota and California, have evolved into first-class schools using state funds; perhaps something similar may be found to meet the present crisis. Those who receive could be as smart as the bureaucrats who give and less politically activated.

Our insurance programs covering medical care are in their infancy, awaiting technics that will meet the need without regimenting the doctors or the people. With time, existing plans will be modified and better programs will receive better support.

The outstanding feature of the past 50 years has been the progress of knowledge which, coupled with high standards of education, has given physicians vast powers over disease.

The improvements in antibiotics, glandular preparations, anesthetics, antispasmodics and anticonvulsants, analgesics and specific remedies have seen one disease after another brought under control. We are still baffled by degenerative disorders and aging. But duration of stay in hospitals has been lessened, infant mortality conquered, and longevity increased wherever medical personnel and facilities have been adequate to a nonindigent population. The problem is one for the application of the American genius for organization and production. I do not mean a Mayo or Crile or Lahey Clinic at every crossroad. I do not think we need a revolution. I mean building as a democracy of cooperative labor, capital, farmers and white collar workers on what we have—because what we have is good. We simply need more of it and the means to use it.

MORRIS FISHBEIN

NEW METHODS IN THE DIAGNOSIS OF POLIOMYELITIS

DR. Karl Landsteiner demonstrated, in 1908, that poliomyelitis could be produced in monkeys and chimpanzees. In 1939, Dr. Charles Armstrong of the Public Health Service's National Institutes of Health in Bethesda, Maryland, adapted, first to cotton rats and then to mice, a strain of virus isolated from a patient in Lansing, Michigan, hence called the Lansing strain and designated as Type II. Soon other strains of virus were isolated with different characteristics, capable of producing a similar disease in man, monkeys or chimpanzees.

At other laboratories other studies, particularly those sponsored by the National Foundation for Infantile Paralysis, separated and differentiated the other two main types—Leon (named for the California patient from whom it was isolated), designated as Type III, and Brunhilde (named for a chimpanzee from which it was isolated, in a Johns Hopkins laboratory), designated as Type I. The three types differ in several ways: Immunity to one type does not confer immunity to the others. When a person suffers a second or third attack of poliomyelitis, his attacks are caused by infection with different types of virus, although the physician finds it impossible to distinguish them. They can be identified and studied only in the laboratory.

After 1939, the Lansing strain could be studied in mice, but the other two types could

be isolated only by using monkeys or chimpanzees. About 6 years ago a group of workers at the Harvard Medical School devised a means by which they could grow the virus in test tubes—the so-called tissue-culture technic. In 1951, Public Health Service workers succeeded, in two steps, in transferring the Leon strain to mice. The first step was made at the National Institutes of Health, by Dr. Li and Dr. Karl Habel, and the second step—a further perfection—was made at the Montgomery center by Dr. Li and Dr. Schaeffer.

Now Drs. Li and Schaeffer report, according to a release from the United States Public Health Service, the adaptation of the Brunhilde strain to mice, by the combination of two virologic technics, the tissue-culture method and the intraspinal inoculation, which means injecting the virus directly into the spinal cord rather than the brain, which has been the usual method up to now.

This discovery makes possible demonstration of the serum antibody response in a patient with poliomyelitis using a relatively simple mouse test. The test will lessen the cost of studies of epidemics. With this method the assessment of the use of gamma globulin and vaccination for the prevention and control of poliomyelitis becomes less difficult.

Research on poliomyelitis has been retarded by the necessity for using monkeys and chimpanzees, of which the supply is limited, the cost expensive and the experiments difficult. The new diagnostic method associated with the tissue-culture method marks significant progress. Indeed, the authors themselves say in their report, "This adaptation, when confirmed by other investigators, will provide the simplified tool with which to conduct, on a more extensive scale, the important field and laboratory studies previously hampered by tedious and expensive methods. The adaptation of the three virus types to mice will permit the performance of rapid, reproducible, and relatively inexpensive diagnostic tests."

One of the functions of the Communicable Disease Center is the training of technicians from the state health departments in new methods and technics; as soon as training facilities at the Montgomery laboratory and elsewhere permit, state and private laboratories should be able to provide this new diagnostic service themselves.

The authors indicate also that the development opens the possibility of preparing a modified active-virus vaccine against poliomyelitis. The clue lies in the demonstration that passage through mice causes the virus to lose its paralyzing effect for monkeys, although it does not impair the ability of the virus to immunize.

These discoveries indicate once more the rapid development of new information and technic once a breach has been opened in a wall of lack of knowledge that still surrounds many diseases such as multiple sclerosis. Our knowledge of poliomyelitis will soon eliminate many hidden areas that still remain.

MORRIS FISHBEIN

CLINICS AND FAMILY DOCTORS

THERE are now some 20 recognized specialties and another 20 offshoots of specialties. Surgeons include brain, nerve, blood vessel, heart, gastroenterologic, orthopedic, urologic, chest and plastic surgeons; ophthalmic, otolaryngologic and oral surgeons.

If group practice is the answer to the problem of a complete medical service, it has made exceedingly slow progress. The number of groups has increased from a few in 1890 to:

239 with 1466 physicians in 1932
335 with 2093 physicians in 1940
368 with 3084 physicians in 1946
500 with 5000 physicians in 1950

A group means 6 to 10 doctors plus equipment and auxiliary personnel. Obviously the whole picture would change if hospitals organized their staffs to deliver service as groups. One of the greatest difficulties observed in the past 40 years has been the tendency of some organized groups to evade the customs and ethics of the medical profession for the acquirement of larger practices and more income.

MORRIS FISHBEIN

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Panthenol, equivalent to of calcium pantothenate	10.0	mg.
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Folic acid	2.0	mg.
Nicotinamide	100.0	mg.
Vitamin E (as mixed tocopherols natural)	10.0	mg.
Inositol	30.0	mg.
Choline—from choline bitartrate	30.0	mg.
Biotin	0.1	mg.
d-Methionine	20.0	mg.
Cobalt—from cobalt sulfate	0.1	mg.
Copper—from copper sulfate	1.0	mg.
Fluorine—from calcium fluoride	0.025	mg.
Iron—from 4 gr. ferrous sulfate exsic.	76.2	mg.
Calcium—from dicalcium phosphate	165.0	mg.
Manganese—from manganous sulfate	1.0	mg.
Iodine—from potassium iodide	0.15	mg.
Molybdenum—from sodium molybdate	0.2	mg.
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THE MEDICAL Bookman

► MODERN TREATMENT; A Guide for General Practice

Edited by Austin Smith, M.D., Editor, Journal of the American Medical Association, *and Paul L. Wermer, M.D., Secretary, Committee on Research, American Medical Association. 53 authors. 1,146 pages. 1953, Paul B. Hoeber, Inc., New York. $20.00.*

In recent years, with the innumerable advances in medicine, it has not been easy for the specialist to stay abreast of the various methods of treatment within his own sphere of interest. At the same time it has become impossible for the general practitioner to keep informed of and to evaluate the countless methods of treatment in all fields of medicine. Recognizing the needs of the general practitioner for an authoritative guide to sound therapy, a group of 53 outstanding specialists under the leadership of Drs. Smith and Wermer have collected in one volume the essentials of present day therapy.

A successful attempt has been made to cover the treatment of every condition which the general practitioner is likely to encounter. The various conditions are conveniently grouped together and individually discussed under general chapter headings such as Bacterial Infections, Heart Disease, Arthritis, Diseases of the Thyroid, Treatment in Obstetrics, Otolaryngologic Disease, Secondary Shock, etc. There are 51 chapters in all. In the discussion of specific conditions, the author of each chapter recommends the treatment which in his judgment is the most effective. In appropriate instances, alternative methods of treatment, supportive measures and guides to duration of treatment are discussed. An excellent chapter on anticoagulant therapy should prove helpful in the treatment of many conditions.

The authors, knowing that intelligent treatment is based on more than mere knowledge of specific measures to apply, have included comprehensive discussions on the general principles of immunology, pharmacology, chemotherapy, psychosomatic illnesses, nutrition, surgical treatment, physical medicine, radiology, anesthesia and inhalation therapy. The appendix contains a list of the normal laboratory values for blood, urine, cerebrospinal fluid and miscellaneous tests. There are also two valuable chapters on the performance and interpretation of the numerous diagnostic technics essential to successful diagnosis and treatment. Well over a hundred technics are discussed, including the circulation time, cold pressor and other tests for hypertension, exercise tests for coronary insufficiency, liver function tests, glucose tolerance tests, adrenal function tests, and so forth.

This book should prove useful to general practitioners and to all physicians who, in the course of their practice, are called upon to treat a diversity of conditions.

R. V. R.

► DISEASES OF METABOLISM

Detailed Methods of Diagnosis and Treatment. Edited by Garfield G. Duncan, M.D., Director of Medical Division, Pennsylvania Hospital; Clinical Professor of Medicine, Jefferson Medical College, Philadelphia. Ed. 3. 1,179 pages, illustrated. 1952, W. B. Saunders Company, Philadelphia & London. $15.00.

Five years have elapsed since the second edition of this book was printed. This half decade has been so fruitful in terms of both basic metabolic research and clinical advances in diagnosis and therapy of metabolic diseases that a third edition was sorely needed.

Dr. Duncan has called on 19 authorities in the various fields of metabolism to assist him in

(Continued on page A-54)

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bringing the material up to date. Many chapters have been entirely rewritten, including those dealing with carbohydrate metabolism, water balance, undernutrition, thyroid disorders and childhood diabetes. The section on vitamins and avitaminosis has been greatly enlarged, and a chapter on porphyrin metabolism by Dr. Cecil J. Watson has been added.

Other new contributors are Drs. Samuel Soskin, Rachmiel Levine, Priscille White, Rulan W. Rawson, J. E. Rall and Ancel Keys.

The general policy of presenting normal and abnormal physiology and biochemistry followed by clinical material has been carried over from previous editions with gratifying results. Each subject is covered in great detail with adequate references to the literature, particularly clinical. Yet much material is presented on the authority of the writer in order to avoid the multitudinous references otherwise required.

Most chapters are liberally provided with helpful tables, figures, diagrams and photographs, both clinical and pathologic. An appendix contains data for determining normal height, weight, growth pattern and basal energy requirements. The book is indexed for authors and subjects.

T. B. G.

► RADIOLOGIC DIAGNOSIS OF THE LOWER URINARY TRACT

By Donald E. Beard, M.D., William E. Goodyear, M.D. and H. Stephen Weens, M.D., Emory University School of Medicine, Atlanta, Georgia. 143 pages with 280 figures. 1952, Charles C Thomas, Springfield, Illinois. $6.50.

Generally speaking the lower urinary tract has been a stepchild of the radiologist. Inasmuch as the urethra lends itself so well to examination by external palpation and with the urethroscope and cystoscope, not much attention has been paid to examining this portion of the urinary tract by the x-ray methods.

This text is in the form of an atlas with excellent roentgenograms demonstrating the anatomy and the pathology of the organs. Some of these illustrations have been improved by drawings of the anatomic structures surrounding the urethra and bladder so that the relationship of the organs not visualized on the x-ray are thus beautifully demonstrated. In examining the urethra the authors use iodized oil. In the illustrations considerable contrast is also shown in the bladder—a very expensive procedure if done routinely with oil. Other authors such as Edling of Sweden recommend the use of a water-soluble contrast material that has been made viscous. This has the added advantage that films made during micturition are possible because this contrast is freely miscible with the urine while the oil is not.

A special chapter on urethrography and cystography in children is included. This is of course of great value as a few special pathologic entities such as congenital valves of the posterior urethra and hypertrophy of the verumontanum are seen almost exclusively in children.

J. F.

► THE HISTORY OF AMERICAN EPIDEMIOLOGY

By C.-E A. Winslow, Dr. P.H., Wilson G. Smillie, M.D., James A. Doull, M.D. and John E. Gordon, M.D. Edited by Franklin H. Top, M.D., Professor of Epidemiology and Pediatrics, University of Minnesota College of Medical Sciences, Minneapolis. 190 pages. 1952, The C. V. Mosby Company, St. Louis. $4.75.

A series of lectures given at the American Public Health Association meeting in New York City in October 1949 provides the basis for this book. The material is most interesting and every medical historian, epidemiologist, bacteriologist and physician can enjoy it. The reviewer wishes that some people who don't believe in disease and germs could read this book and learn what scientific medicine has done to benefit them.

For instance, in 1878 an epidemic of yellow fever raged in Memphis, Tennessee. Out of the city's 50,000 inhabitants some 30,000 fled, and of those who remained 5,150 died. Of 39 volunteers who stayed to help the sick, 32 were attacked and 12 died. That sort of thing used to happen at intervals in the cities throughout the South, and even in Philadelphia. The last great epidemic of yellow fever was in 1905; it struck in Galveston and New Orleans. Today, of course, there can be no yellow fever in Memphis because

(Continued on page A-56)

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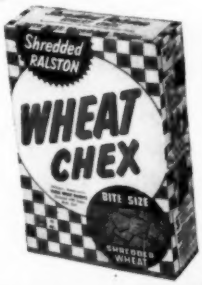

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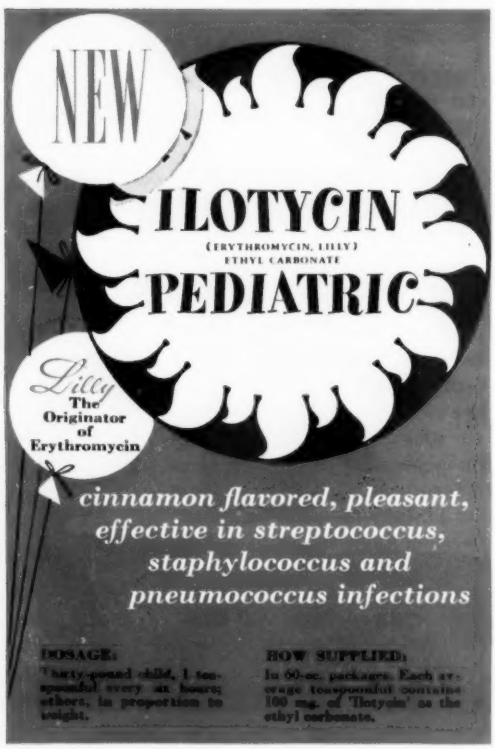
the mosquitoes are gone. If there are a few left they cannot get infected with yellow fever, and if conceivably yellow fever should start, it could be stopped quickly with vaccination.

The sad point that is brought out repeatedly in this little book is that often for 50 years or so after it was obvious that serious epidemics could be avoided in some simple way, the people did nothing, or even blocked the efforts of doctors to improve matters. For that matter, even today, if a referendum were to be taken on the subject, in many cities nearly half the people would follow the lead of faith healers, crackpots and quacks, and demand that they be permitted again to have smallpox and typhoid fever.

W. C. A.

► CLINICAL ELECTROCARDIOGRAPHY IN CHILDREN

By Gertrude H. B. Nicolson, M.D., Instructor in Pediatrics, Columbia University. 118 pages with 58 figures. 1953, The Macmillan Company, New York. $3.25.



The reviewer has often wondered what the electrocardiogram is like in children, and whether it is often necessary to make such a record in the case of a child; he wondered what it might show. All the answers to these questions can be found in this little book. Doubtless it will be welcomed by pediatricians and experts in heart disease. It was written by the chief of the Children's Cardiac Clinic at St. Luke's Hospital in New York City. The average child's electrocardiogram follows a simple pattern which can be recognized as that of a normal child. The text is well illustrated.

W. C. A.

► THE PRINCIPLES OF NEUROLOGICAL SURGERY

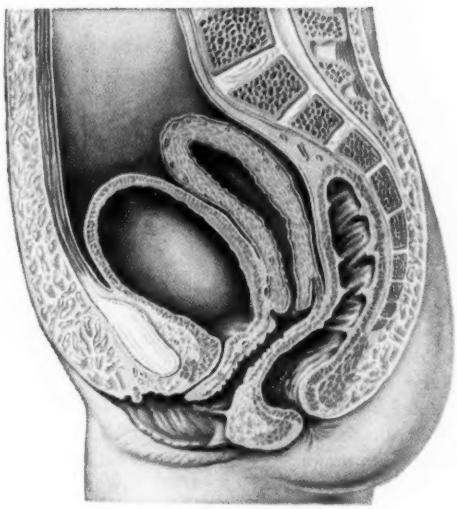
By Loyal Davis, M.D., Professor of Surgery. Northwestern University Medical School, Chicago. Ed. 4. 544 pages with 186 figures. 1953, Lea & Febiger, Philadelphia. $8.50.

Like its predecessors, this fourth edition of Dr. Davis' book deals with the general principles of neurologic surgery as applied to general diagnosis, therapy and prognosis. Additions include material on the use of radioactive isotopes, of angiography and of some of the recent developments in treatment. Otherwise, there is very little change from the preceding edition. Most of the previously present inconsistencies and contradictions have again been included. It is presumed that the magnitude of the production has prevented revision of this somewhat confusing editorial style. This is unfortunate for the book is written primarily as a text for medical students and this style detracts from its usefulness.

The book is comprehensive. It deals with all the important neurosurgical lesions. Dr. Davis has made a determined effort to present the material from a clinical viewpoint. He has included all necessary neuroanatomic and neurophysiologic data required to understand properly the clinical development of the lesion and the scheme of therapy. He begins with a thoroughly instructive chapter on the technic and significance of the neurologic examination. Thereafter, the various lesions of the nervous system are discussed. These include injuries, tumors and infections of the skull, brain, spinal cord and peripheral nerves. The remainder of the book includes material on the treatment of intractable

(Continued on page A-58)

Preventing Postpartum Urinary Retention



In a recent study,[1] the prophylactic administration of URECHOLINE to 129 postpartum patients reduced the incidence of urinary retention from a previously reported 13.8 to 2.3 per cent. Therapeutic use of the drug successfully relieved acute urinary retention in 46 per cent of 73 cases.

[1] Fleming, A. R.: *Am. J. Obst. & Gyn.* **64**: 134, 1952

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pain, sympathetic nerve surgery, surgery of the convulsive disorders, vascular malformations, anomalies of the neural axis, psychoses and on abnormal involuntary movements. These last chapters, in particular, round out this edition and enhance its value.

This book is not intended as a reference work. An adequate bibliography is presented, but the opinions expressed are primarily those of the author. The illustrations all seem well selected and the volume itself is printed on high-grade paper and excellently bound.

L. A. F.

► POST-GRADUATE LECTURES ON ORTHOPEDIC DIAGNOSIS AND INDICATIONS

By Arthur Steindler, M.D., Professor of Orthopedic Surgery, State University of Iowa, Iowa City. Vol. 4. 312 pages with 276 figures. 1952, Charles C Thomas, Springfield, Illinois. $9.75.

This fourth volume of a distinguished encyclopedic series on orthopedic diagnosis and treatment has recently become available. Similar to the previous editions in arrangement and form, the final volume completes a monumental endeavor and is a fitting tribute to the encompassing knowledge of the author. The subject matter contains profound observations on the arthritides and associated diseases of the muscles, bursae, tendons and fasciae. In addition, a review of the deficiency and degenerative diseases of the locomotor system is included. Volume 4 has the same clear, concise commentary that features the series generally and accounts for one of its outstanding qualities.

Many readers may, on occasion, find reason to debate the accepted conclusions. This factor, however, does not tend to derogate but rather to stimulate aggressive perusal and judicial thought.

Actually, there are more illustrations than text pages. The pictures, radiographic reprints and photomicrographs have been carefully chosen; they form a splendid background for the descriptive writing.

It seems likely that this contribution will find its way to the libraries of active orthopedic surgeons. Other practitioners will recognize its value for quick reference studies.

H. O'P.

► GIFFORD'S TEXTBOOK OF OPHTHALMOLOGY

By Francis Heed Adler, M.D., Professor of Ophthalmology, University of Pennsylvania School of Medicine, Philadelphia. Ed. 5. 488 pages with 281 figures and 26 color plates. 1953, W. B. Saunders Company, Philadelphia & London. $7.50.

In this fifth edition, Dr. Adler has considerably enlarged the sections on hypertensive disease and diabetes. Much new material has been added, particularly in the field of therapeutics. This was necessary because of the recent developments in the use of antibiotics and ACTH and cortisone.

The book has been designed as a practical manual for the general physician, and for this it would appear to be ideal.

W. C. A.

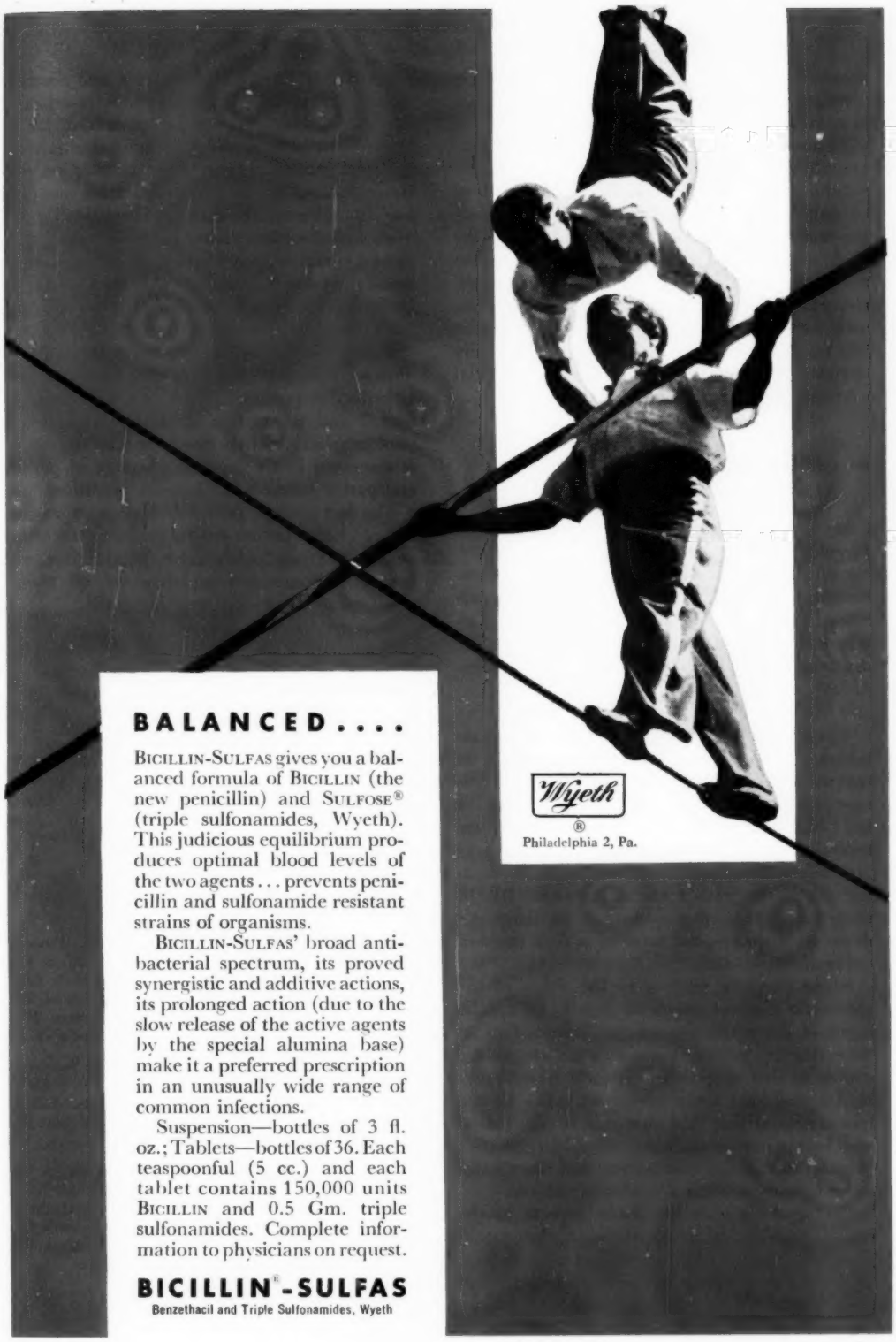
► HANDBOOK OF ORTHOPAEDIC SURGERY

By Alfred Rives Shands, Jr., M.D., Medical Director, Alfred I. duPont Institute de Nemours Foundation, Wilmington, Delaware, in collaboration with Richard Beverly Raney, M.D., Professor of Orthopedic Surgery, University of North Carolina, Chapel Hill, North Carolina. Ed. 4. 644 pages with 192 illustrations. 1952, The C. V. Mosby Company, St. Louis. $8.00.

Previous editions of this publication are well known to those interested in the field of orthopedic surgery. The advent of a new revision will receive immediate and wide acceptance; it has been made necessary by the inevitable advancements in this division of surgery. One of the prime difficulties in preparing a textbook lies in the maintenance of an up-to-date bibliography. By the time a book reaches appropriate bookstands, more recent contributions have become available in the contemporary magazines. This is a recognized fact and does not detract from the value of the material presented.

Indeed, with brief but concise discussions the text is a definite improvement over earlier editions. It is well organized with adequate consideration afforded all pertinent subjects. Already established as one of the better textbooks in the orthopedic realm, certain deletions are

(Continued on page A-60)



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necessary so that this book may be kept to a manageable size. The primary intention has been to convey precise information in a manner that will not overburden the undergraduate and busy practitioner. This theme is dominant throughout the entire fourth edition. Critical evaluations by outstanding men in bone and joint surgery are timely and tend to increase the value of the book. Subjects of contemporary interest have been added but elaboration of material available elsewhere has not been sustained. The intention of the author to avoid detail precludes this feature. Such gaps in knowledge are easily obviated by the excellent reference material catalogued in the bibliography.

H. O'P.

► COMROE'S ARTHRITIS AND ALLIED CONDITIONS

Completely revised and rewritten. Edited by Joseph Lee Hollander, M.D., Associate Professor of Medicine and Chief of Division of Rheumatology, Graduate School of Medicine, University of Pennsylvania, Philadelphia. With 17 Collaborating Editors. Ed. 5. 1,103 pages with 399 illustrations. 1953, Lea & Febiger, Philadelphia. $16.00.

The fifth edition of this standard volume establishes it as the outstanding text available on the rheumatic diseases. Due to the rapid advances over the past few years extensive revision has been required of the 1949 edition. There are several entirely new chapters and a total of 93 new illustrations have been added; yet the overall size of the book remains the same. All 18 contributors are active workers in the rheumatic diseases; therefore, the material is both authoritative and up-to-date.

Seven chapters relating to the study of the rheumatic diseases comprise part 1. Of special merit is the discussion of the examination of the arthritic patient. Careful attention to the details of this chapter will greatly repay every reader and help make unnecessary the all too true statement that "the physician is rare indeed who knows how to examine joints." Dr. Smyth's chapter on radiology enlightens and contributes order to what is often a confusing subject.

Part 2 deals with the many aspects of the major problem in rheumatology: rheumatoid arthritis. A chapter by Freyberg on steroid therapy is an excellent summary and evaluation of the vast literature on this current and complex matter. Hollander's chapter on the intra-articular use of hydrocortisone will be appreciated for its practical nature and for the helpful illustrations.

Part 3 contains an excellent chapter on psychogenic rheumatism. A helpful table summarizes its differentiation from fibrositis. Part 4 deals with disorders related to rheumatoid arthritis and contains good discussions on rheumatoid spondylitis by Boland and rheumatic fever by Holbrook. A chapter on fibrositis by Graham adds clarity to a controversial entity.

Parts 5 and 6 adequately cover the collagen diseases and degenerative joint disease (osteoarthritis) respectively. Gout is well covered in part 7 and the text is illustrated by excellent photographs. Arthritis due to specific infections is discussed in six separate chapters of part 8, and part 9 covers miscellaneous conditions.

The last section, part 10, deals with various disorders that border on the realm of the orthopedist. The painful shoulder, painful feet, and backache—common complaints we all should know more about—are well presented.

P. J. B.

Books received will be acknowledged in this department each month. As space permits, books of principal interest to our readers will be reviewed more extensively.

The Roentgen Aspects of the Papilla and Ampulla of Vater. By Maxwell H. Poppel, M.D., Professor of Radiology; Harold G. Jacobson, M.D., Associate Clinical Professor of Radiology, New York University Post-Graduate Medical School, New York; and Robert W. Smith, M.D., Senior Resident in Radiology, Veterans Administration Hospital, Bronx, New York. 195 pages with 106 figures. 1953, Charles C Thomas, Springfield, Illinois. $8.50.

The Physical Examination of the Surgical Patient. By J. Englebert Dunphy, M.D., Associate Clinical Professor of Surgery, and Thomas W. Botsford, M.D., Clinical Associate in Surgery, Harvard Medical School, Boston, Massachusetts. 326 pages with 188 figures. 1953, W. B. Saunders Company, Philadelphia & London. $7.50.

Morris' Human Anatomy; A Complete Systematic Treatise. By J. Parsons Schaeffer, M.D., The Jefferson Medical College, Philadelphia, Pennsylvania. Ed. 11. 1,718 pages with 1,220 figures. 1953, The Blakiston Company, New York. $16.00.

Chronic Alcoholism and Alcohol Addiction; A Survey of Current Literature. Brookside Monograph No. 1. By R. J. Gibbins with the assistance of B. W. Henheffer and A. Raison, Department of Psychology, Queen's University, Kingston, Ontario. 57 pages. 1953, Alcoholism Research Foundation, Toronto, Canada. $1.50.

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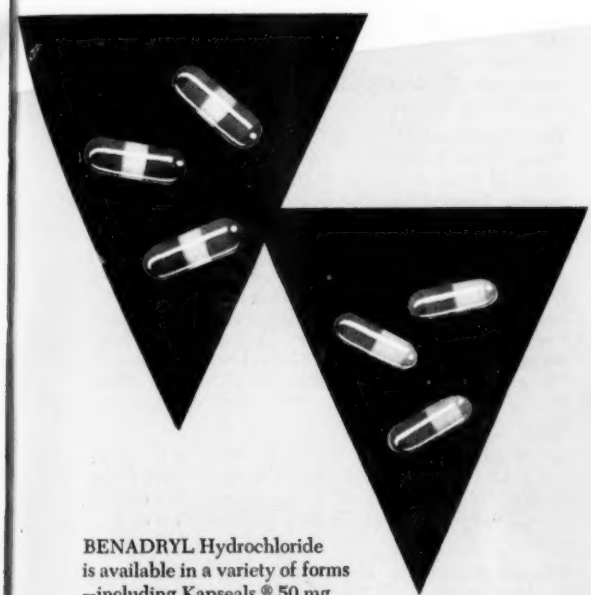

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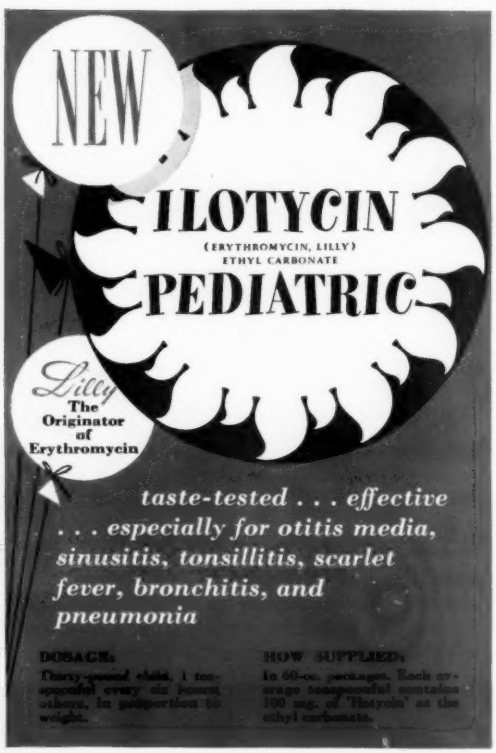
It All Started with Columbus; An Improbable Account of American History. By Richard Armour, Professor of English, Scripps College, Claremont, California. 115 pages, illustrated. 1953, McGraw-Hill Book Company, Inc., New York. $2.75.

Modern Concepts of Leprosy. By Harry L. Arnold, Jr., M.D., Department of Dermatology, Straub Clinic, Honolulu, Hawaii. 105 pages with 33 figures. 1953, Charles C Thomas, Springfield, Illinois. $3.75.

Human Blood Coagulation and Its Disorders. By Rosemary Biggs, M.D., Graduate Assistant, Department of Pathology, Radcliffe Infirmary, and R. G. MacFarlane, M.D., Clinical Pathologist to the Radcliffe Infirmary, Oxford, England. 406 pages with 57 figures. 1953, Charles C Thomas, Springfield, Illinois. $8.00.

Sacral Nerve-Root Cysts: Another Cause of the Sciatic or Cauda Equina Syndrome. By I. M. Tarlov, M.D., Professor of Neurology and Neurosurgery, New York Medical College, New York. 134 pages with 65 figures. 1953, Charles C Thomas, Springfield, Illinois. $6.50.

Office Orthopedics. By Lewis Cozen, M.D., Assistant Professor of Orthopedic Surgery, College of Medical Evangelists, Los Angeles. Ed. 2, revised. 304 pages with 191 illustrations. 1953, Lea & Febiger, Philadelphia. $5.50.



Contact Dermatitis. By George Waldbott, M.D., Senior Physician, Harper Hospital, Detroit, Michigan. 218 pages with 332 illustrations. 1953, Charles C Thomas, Springfield, Illinois. $8.75.

Diseases of the Digestive System. Edited by Sidney A. Portis, M.D., Associate Clinical Professor of Medicine, University of Illinois Medical School, Chicago, Illinois. 57 contributors. Ed. 3, revised. 1,119 pages with 269 engravings and 5 color plates. 1953, Lea & Febiger, Philadelphia. $20.00.

Transactions of the American Goiter Association. 1952 Annual Session, St. Louis, Missouri. 429 pages, illustrated. 1953, Charles C Thomas, Springfield, Illinois. $12.50.

Transactions of the American College of Cardiology. Edited by Bruno Kisch, M.D. 252 pages, illustrated. 1953, American College of Cardiology, New York. $5.00.

The Roots of Psychotherapy. By Carl A. Whitaker, M.D., Professor of Psychiatry and Chairman of the Department, and Thomas P. Malone, M.D., Assistant Professor of Psychiatry and Director of Research, Department of Psychiatry, Emory University School of Medicine, Emory University, Georgia. 236 pages with 8 figures. 1953, The Blakiston Company, New York. $4.50.

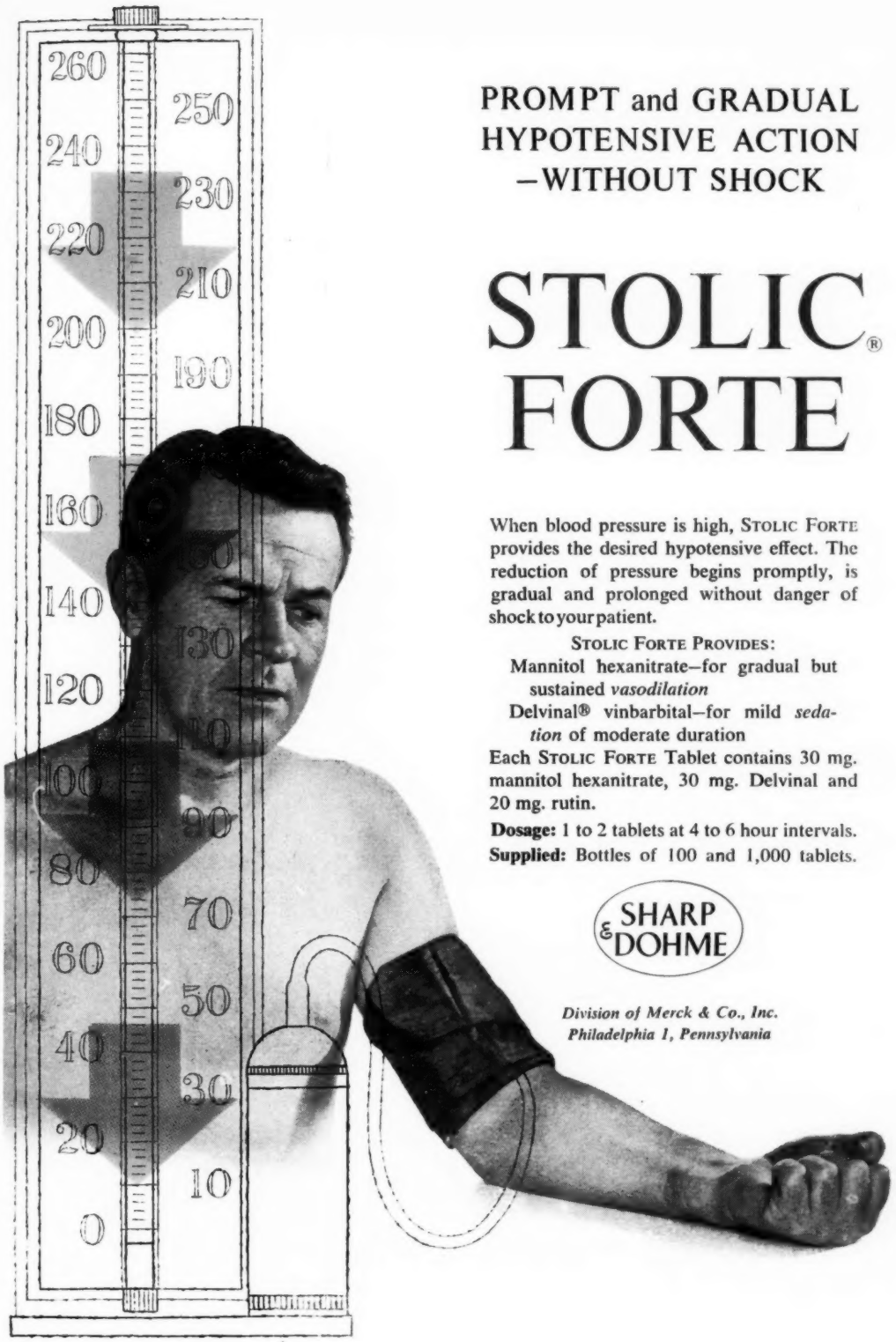
Renal Cortical Necrosis of the Kidney and Concealed Accidental Haemorrhage. By H. L. Sheehan, M.D. and H. C. Moore, M.D., Department of Pathology, University of Liverpool, England. 186 pages with 64 figures and 11 tables. 1953, Charles C Thomas, Springfield, Illinois. $7.75.

The Founders of Neurology; One Hundred and Thirty-Three Biographical Sketches. By 84 authors. Edited by Webb Haymaker, M.D., Chief, Neuropathology Section, Armed Forces Institute of Pathology, Washington, D.C. 479 pages, illustrated. 1953, Charles C Thomas, Springfield, Illinois. $10.50.

An Atlas of Surgical Exposures of the Extremities. By Sam W. Banks, M.D., Associate Professor of Orthopedic Surgery, and Harold Laufman, M.D., Associate Professor of Surgery and Director of Experimental Surgery, Northwestern University Medical School, Chicago. 391 pages with 552 illustrations on 179 plates. 1953, W. B. Saunders Company, Philadelphia & London. $15.00.

Stress and Disease. By Harold G. Wolff, M.D., Professor of Medicine (Neurology), Cornell University Medical College, New York. 199 pages with 39 illustrations. 1953, Charles C Thomas, Springfield, Illinois. $5.50.

Clinical Diagnosis by Laboratory Methods: A Working Manual of Clinical Pathology. By James Campbell Todd, M.D., Late Professor of Clinical Pathology, University of Colorado School of Medicine, Denver; Arthur Hawley Sanford, M.D., Emeritus Professor of Clinical Pathology, Mayo Foundation, Rochester, Minnesota, and Benjamin B. Wells, M.D., Professor of Medicine, University of Arkansas School of Medicine. Ed. 12. 998 pages with 946 illustrations, 197 in color. 1953, W. B. Saunders Company, Philadelphia & London. $8.50.



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